THE UNIVERSITY
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IMPACT, A VALIDATED, COMPREHENSIVE CORONARY HEART DISEASE MODEL

OVERVIEW & TECHNICAL APPENDICES

Simon Capewell, Julia Critchley & Belgin Unal

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A SUMMARY OF THE IMPACT CHD MODEL RESEARCH PROGRAMME (1996 onwards)

INTRODUCTION

Coronary heart disease (CHD) is the largest cause of mortality in most industrial countries. CHD is also rapidly increasing in many developing countries.

However, CHD mortality rates have been falling since the 1970s in the UK, and in many other developed countries,. These trends need to be explained in order to explore different policy options for CHD prevention.

OBJECTIVES

The objectives of this research programme are:

1. To document and critically review CHD data, and define the burden of CHD mortality and morbidity in a variety of countries (England and Wales, Scotland, New Zealand, Finland, the USA, Australia, Italy, Sweden, China, Hong Kong and elsewhere;
2. To explain most of the recent falls in CHD mortality in these countries (and rises in countries such as China);
3. To estimate the life-years gained by modern cardiological treatments, and by changes in cardiovascular risk factor levels;
4. To examine the potential benefits of increasing the uptake of cardiological treatments;
5. To estimate the potential benefits of reducing cardiovascular risk factors
6. To calculate the cost-effectiveness ratios of these interventions
7. To continuously improve, refine and develop the IMPACT Model.

METHODS

In each country, all potentially relevant CHD data are identified, critically reviewed, used to assess the burden of disease and then used to create an IMPACT CHD Model for that particular population. The main data sources include official statistics, clinical audits, national surveys and peer-reviewed publications.

The cell-based IMPACT Mortality Model has been extensively developed and refined to better synthesise data for each specific country describing:

a) CHD patient numbers, b) uptake (use) of specific medical and surgical treatments,

c) treatment effectiveness (mortality reduction), d) population trends in major cardiovascular risk factors, e) effectiveness of risk factor changes (change in mortality), using published trials and meta-analyses f) median survival in specific groups of patients and healthy subjects, and costs of specific interventions.

All data and analyses are routinely stratified by ten year age groups in men, and in women.

Sensitivity analyses using Brigg's 'Analysis of extremes' approach are then performed in each study.

RESULTS

1. England and Wales (1981-2000)

CHD data were surprisingly patchy and mixed in quality. In 2000, an iceberg of disease was demonstrated in the England and Wales population of 51million, with approximately 60,000 patients undergoing revascularisation each year, almost 3 million patients living with CHD and over 32 million possessing one or more elevated risk factors.

Between 1981 and 2000, England and Wales CHD mortality rates fell by 62% in men and 45% in women aged 25-84. This resulted in 68,230 fewer deaths in 2000, when compared with the 1981 baseline. Approximately 42% of this mortality fall was attributable to treatments in individuals (including 8% from initial treatments of acute myocardial infarction, 11% from secondary prevention, 13% from heart failure treatments, and 3% from hypertension treatments). Some 58% of the mortality fall was attributable to population risk factor reductions (principally smoking 48%, blood pressure 9.5% and cholesterol 9.6%). Adverse trends were seen for obesity, diabetes and physical activity. Overall, the model explained approximately 96% of the mortality fall in men, and 79% in women. *[Unal et al, Circulation 2004]*

The 68,230 deaths prevented or postponed in 2000 corresponded to approximately 994,610 **life-years gained.** Specific treatments for CHD patients gained approximately 194,145 life-years *(minimum estimate 142,500, maximum estimate 259,220).* Population changes in the major risk factors (smoking, cholesterol, blood pressure) accounted for over three times as many life-years gained *(*approximately 800,465, *minimum estimate 602,690, maximum 879,420).* Adverse changes in physical activity, obesity and diabetes resulted in a loss of approximately 92,600 life-years *(minimum 68,350, maximum 100,760). [Unal et al, Am J PH 2005]*

In 2000, all medical and surgical CHD treatments together prevented or postponed approximately 25,760 deaths. However, treatment uptakes were generally poor, only 30% - 60% of eligible patients were receiving appropriate therapies. Increasing treatment uptake to reach 80% of eligible patients (the NSF CHD target) would have prevented or postponed approximately 20,910 further deaths *(minimum 11,030, maximum 33,495),* almost doubling the actual gain from therapies.

Using 2000 as the baseline, continuation of recent risk factor trends should result in approximately 15,145 fewer coronary deaths in 2010 *(min 12,170, max 17,290).* However, achieving the modest additional risk factor reductions already seen in the USA and Scandinavia could potentially result in approximately 51,185 fewer deaths in 2010 *(minimum 39,395, maximum 72,330). [Unal et al, J Clin Epid]*

COMMENTS

2. Scotland (1975-1994)

There were 15,234 CHD deaths in 1994 in the whole Scottish population of 5.1 million, 6,205 fewer deaths than expected if there had been no decline from 1975 mortality rates. (a 34% fall overall). In 1994, the total number of deaths prevented or postponed by all treatments and risk factor reductions was estimated by the IMPACT Model at approximately 6747, *(minimum 4790, maximum 10695).* Some forty percent of this benefit was attributed to treatments (initial treatments for acute myocardial infarction 10%, treatments for hypertension 9%, for secondary prevention 8%, for heart failure 8%, aspirin for angina 2%, CABG surgery 2% and angioplasty 0.1%).
Approximately fifty one percent of the reduction in deaths was attributed to measurable risk factor reductions. (Smoking 36%, cholesterol 6%, the secular fall in blood pressure 6% and changes in deprivation 3%). Other, unquantified factors apparently accounted for the remaining 9%. These proportions remained relatively consistent across a wide range of assumptions and estimates in a sensitivity analysis. *[Capewell et al, Heart 1999]*

3. New Zealand (1982-1993)

In Auckland, New Zealand, (population 996,000), there were 557 fewer CHD deaths in 1993 compared with 1982 mortality rates. Half the mortality fall (48%) was attributable to medical treatments, [mainly for myocardial infarction, secondary prevention, hypertension and heart failure]. The remaining 52% was attributable to risk factor reductions, principally smoking.
In Scotland, there were 6203 fewer CHD deaths in 1994 compared with 1975 mortality rates. These proportions remained relatively constant using a robust sensitivity analysis, and were consistent with comparable studies in USA and Holland. *[Capewell et al, Circulation 2000]*

4. Finland (1982-1997)

Finland has been a very active country in coronary heart disease prevention since the 1970s when the coronary mortality was one of the highest in the world. Based on active programs coronary heart disease mortality has been declining in Finland since 1960s. Decline in serum cholesterol, blood pressure and smoking explained almost all the decline in mortality during the 1970s. Since the 1980s mortality has declined more than might be predicted by risk factor declines alone.

The aim of this study was to assess how much of the fall in coronary heart disease (CHD) mortality can be attributed to medical treatments, and how much to cardiovascular risk factor reductions.

Cardiovascular risk factors were measured in independent random samples in 1982 and 1997 in three areas in Finland: North Karelia province, Kuopio province and south west Finland. The sample sizes for population aged 35 to 64 years in three areas were 8501 in 1982 and 4500 in 1997 and the total population aged 35 to 64 years in the same areas was 250 000. Treatment data on cardiac patients and mortality data were obtained from myocardial infarction registers, the national mortality register, patient medical records and Social Security registers.

Between 1982 and 1997, CHD mortality rates fell by 63%, with 373 fewer CHD deaths than expected from baseline mortality rates in 1982. The IMPACT model explained 78-96%% of this fall. Contribution of improvements in treatments to CHD mortality reduction was 25% [*acute myocardial infarction 3%; secondary prevention 10%, heart failure 2%, and angina 10%],* and 53% to risk factor reductions *[cholesterol 37%, smoking 9%, population blood pressure 7%]*

These findings emphasise the importance of a comprehensive strategy which promotes primary prevention programmes, particularly for diet, smoking, and blood pressure reduction and which also actively supportssecondary prevention programmes, and maximise the population coverage of effective treatments. *[Laatikainen et al, 2005]*

5. Ireland (1985-2000)

Between 1985 and 2000, CHD mortality rates in Ireland fell by 47% in both men and women aged 25-84. The *'observed'* fall in deaths and the reduction *estimated* from the model in 2000 compared with 1985 were 3763 and 3632 respectively. Some 48.8% of the observed decrease in mortality was attributed to treatment effects, including 18.0% secondary prevention, 14.0% heart failure 8.4% chronic angina, 4.5% initial treatments of acute myocardial infarction and 1.6% hypertension treatments. Approximately 47.7% of the observed mortality fall was attributable to favourable population risk factor trends; specifically declining smoking prevalence (25.6%), and falls in mean cholesterol concentrations (29.8%) and blood pressure levels (6.0%). These trends were partially offset by increases in adverse population trends related to obesity, diabetes and inactivity (- 13.8%). [Kabir et al, 2006]

6. Beijing, China

Coronary heart disease (CHD) mortality is rising in many developing countries. We examined how much of the increase in CHD mortality in Beijing between 1984–1999 could be attributable to changes in major cardiovascular risk factors, and assessed the impact of medical and surgical treatments.

Methods and Results: A validated, cell-based mortality model synthesised data on: a) patient numbers, b) uptake of specific medical and surgical treatments, c) treatment effectiveness, d) population trends in major cardiovascular risk factors (smoking, total cholesterol, blood pressure, obesity, and diabetes). Main data sources: WHO MONICA and Sino-MONICA studies, Chinese Multi-provincial Cohort Study, routine hospital statistics and published meta-analyses.

Age-adjusted CHD mortality rates increased by approximately 50% in men and 27% in women (1608 more deaths in 1999 than expected applying 1984 rates). Most of this increase (around 77% or 1397 additional deaths) was attributable to substantial rises in total cholesterol levels (over 1 mmol/l), plus increases in diabetes and obesity. Blood pressure decreased slightly, while smoking prevalence increased in men but decreased substantially in women.

In 1999, medical and surgical treatments in patients together prevented or postponed approximately 642 deaths, mainly from initial treatments for acute myocardial infarction (approximately 41%), hypertension (24%), angina (15%), secondary prevention (11%), and heart failure (10%). Multi-way sensitivity analyses did not greatly influence the results.

Much of the dramatic CHD mortality increases in Beijing can thus be explained by rises in total cholesterol, reflecting an increasingly 'Western' diet. Without cardiological treatments, increases would have been even greater. *[Critchley et al, 2005]*

CONCLUSIONS

Coronary heart disease represents a massive burden of disease in the UK, and in most industrialised countries. Recent falls in CHD mortality rates reflect a combination of risk factor improvements and modern therapies.

However, much greater mortality reductions appear possible. Future strategies should therefore maximise the delivery of appropriate therapies to all eligible CHD patients. Most crucially however, effective policies for healthy nutrition and tobacco control might potentially halve current CHD deaths in England and Wales.

Similarly substantial benefits might be expected in many other countries.

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LIST OF ABREVIATIONS

ACE	Angiotensin converting enzyme
AMI	Acute myocardial infarction
BRHS	British Regional Heart Study
BMI	Body mass index
CABG	Coronary artery bypass graft
CHD	Coronary heart disease
CPR	Cardiopulmonary resuscitation
CVD	Cardiovascular disease
DALY	Disability adjusted life years gained
DPPs	Deaths prevented or postponed
HDL-C	High density lipoprotein cholesterol
HES	Hospital Episode Statistics
HSE	Health Survey for England
LDL-C	Low density lipoprotein cholesterol
LYG	Life years gained
NHS	National Health Service
OR	Odds ratio
PAR	Population attributable risk
PG IIb/IIIa	Platelet glycoprotein IIb/IIIa inhibitors
PTCA	Percutaneous transluminal coronary angioplasty
QALY	Quality adjusted life years
RCT	Randomised controlled trial
RR	Relative Risk
UK	United Kingdom
US	United States

IMPACT CHD POLICY MODEL

INTRODUCTION

1.1 AIM

To achieve a refined coronary heart disease model, which

a) explains most of the recent fall in CHD mortality in England and Wales

b) quantifies the years of life gained by such mortality falls,

c) explores potential gains from medical and surgical treatments and

d) compares potential gains from future changes in cardiovascular risk factors

in order to explore future policy options for CHD prevention.

1.2 OBJECTIVES

1. To identify, select and review critically CHD data from various national and local UK sources
2. To define the burden of CHD in England and Wales using the existing data
3. To update and transform the original Scottish IMPACT Model (1975-94) into an English IMPACT Model, and incorporate relevant English and Welsh data.
4. To explore, test and develop a variety of methodological refinements to the existing CHD IMPACT Model, including:
   - reviewing β coefficients for smoking, cholesterol and blood pressure
   - seeking β coefficients for diabetes, obesity and physical activity
5. To explain most of the recent falls in CHD mortality in England and Wales
6. To estimate the life-years gained attributable to modern cardiological treatments, and to changes in cardiovascular risk factor levels.

7. To estimate the potential benefit of increasing the uptake of effective cardiological treatments.

8. To estimate the potential for cardiovascular risk factor changes to reduce CHD deaths in England and Wales by 2010.

MODELLING

(from Belgin UNAL's PhD Thesis, University of Liverpool 2004)

"All models are wrong but some are useful" (G.E.P. Box, 1978)[207]

Improving population health through effective interventions remains the fundamental challenge for public health practitioners and policy makers. Decision-makers at the population, clinical, and individual levels often need to choose the 'best intervention' for a health problem. However, limitations on resources, time and information can make the decision process very complex. Assessing the value of a health intervention requires consideration of many elements including the size of the target population, the prevalence of the disease, and the intervention's effectiveness and cost[208].

Models are tools that potentially allow users to take into account all these points together and evaluate the intervention options.

1.3 What is a model and why are models used?

A model is a simplification of reality. Models range widely, from simple, descriptive tools (such as a plan of a house), to systems of mathematical equations, which can explain past disease trends[209;210], or which predict future events such as disease epidemics[211;212]. Models are also widely used in environmental surveillance[213] and predicting impact of natural disasters[214]. Such models, therefore, intend to increase understanding, facilitate prediction, or assist in decision making[209].

Weinstein et al recently defined a model as an **'analytic methodology that accounts for events over time and across populations, based on data drawn from primary or secondary sources, whose purpose is to estimate the effects of an intervention on valued health consequences and costs'**[215]. In other words, a model is a logical mathematical framework that permits the integration of facts and values, and which links these data to outcomes that are of interest to health-care decision makers. Models can thus potentially synthesize available evidence on risk factors, health outcomes and costs from many different sources, including data from clinical trials, observational studies, case registries, surveys and routine health statistics[216].

Models are used to guide, or even dictate, policy decisions in many areas that affect human life and health[215]. Increasing health care demands require policy decisions based on good evidence, particularly since resources are usually limited. By openly and explicitly combining local data with trial based effectiveness evidence, models can offer increased transparency to the decision making process (particularly if their assumptions are clearly stated).

Models can also allow a large amount of evidence to be considered simultaneously; by combining and integrating into a coherent whole different types of data from controlled trials, routine surveillance and expert consensus[3]. Models have been extensively used in policy making and resource allocation, since they permit policy makers to examine future policy options, or to simulate the effects of different scenarios within a population[217]. However, improved technology potentially allows both practitioners and policy-makers to use these models, without necessarily understanding the modelling assumptions or the limitations of the data[3].

1.4 General types of models

There are many models in the health literature. They differ greatly in their methods.

Models can be classified in many different ways, based on their intended use (descriptive or prescriptive), their use of probabilities (descriptive, deterministic or probabilistic)[218], their analytical methodology (a decision tree or state transition model), their application to a population (longitudinal or cross-sectional), or their purpose (risk assessment, cost, effectiveness etc.). However these classifications are not mutually exclusive, and a model can therefore belong to more than one classification.

INTENDED USE OF MODEL

Descriptive models are designed to predict or illustrate the result of a clinical process. **Prescriptive models** are used to compare two or more interventions to estimate the optimal treatment option[209]. With respect to intended use, Weinstein also distinguishes between **clinical decision models**, designed to guide clinicians or patients, and **health policy models**, which will help decision makers or organisations with choosing the appropriate strategy and allocating healthcare resources[219].

USE OF PROBABILITIES

Models can be classified into two broad groups based on their use of probability. **Deterministic models** use probabilities based on fixed-point estimates. Thus, the probability experienced in a branch is a single fixed value. However, in **stochastic (probabilistic) models,** the probability of experiencing a certain condition is not a single fixed value but a range of values from a defined distribution. Deterministic models are simpler, require less expertise to develop and can be run on less complex computer softwares[220]. The majority of models are used to evaluate health care costs and outcomes are deterministic.

The analytical methodology

Models can also be classified according to their use of time. Simple **decision trees** are very useful for modelling if the events or health states do not occur repeatedly and the likelihood of the event does not change over time. This modelling approach fits very well for acute conditions such as bacterial infection, antibiotic therapy or adverse events in a hospitalised patient. **Recursive trees** involve treatment patterns or health states that can repeat over time. The model starts with a cohort of individuals and follows them for a period. In each year, individuals have a risk (probability) of developing the outcome. The probability of developing the outcome may change every year, but otherwise each year is a single decision tree. **Markov Modelling** and other **state transition models** are the logical extension of recursive trees for more complex events occurring over time[221]. One limitation of Markov models is that they do not have memory; therefore the chain of preceding events does not influence the likelihood of a given event at a specified time. This limitation could be important for certain clinical outcomes, for example the likelihood of a major depressive patient experiencing an acute episode may depend on the number and timing of previously experienced depressive episodes[220]. In general, recursive trees and Markov models are more complex than decision trees models and require more effort, time and expertise.

LONGITUDINAL AND CROSS-SECTIONAL MODELS

All models include a population or group to estimate the outcomes. **Longitudinal models** calculate expected outcomes for 'typical' patients or cohorts and follow them longitudinally through time to evaluate health outcomes resulting from alternative interventions[218]. It is therefore not possible to take into account demographic trends in

the population or changes in treatment practice[217]. This approach is used more in decision tree models, and outcomes might for instance be QALYs.

Cross-sectional models record the health outcomes of a cross-section of an entire population or substrata, and then follow each person until the end-point of the analysis[218]. The main difference between the two is that cross-sectional models are based on the general population (stratified into different age and sex groups) whereas longitudinal models are based on a cohort of identical subjects. For instance, patients who survived MI and now eligible for statin therapy could be used to assess cost-effectiveness of this therapy in secondary prevention.

The unit of the model on which estimations are based

Models can be divided into two large groups, working on groups or at the individual level. Spreadsheet or cell based models generally work on groups of individuals whereas microsimulation models work on individual level. Since this difference is the main determinant of the outcomes and estimations, these models need to be considered here in more detail.

Microsimulation models (for example CHD Policy Model[222], POHEM[210], Mui's Model[223], and CHD Policy Analysis[224]) can simply project future outcomes for a given individual, based on his or her sociodemographic, behaviour, and clinical characteristics. Here, data from different observational studies such as Framingham Heart study are used for risk estimates.

Microsimulation models could start with a representative sample or subsample of individuals from a census or survey. They can be developed using an entirely synthetic population, which resembles the population of interest. In this process, each individual in the cohort is generated separately, and can be subjected to the probability of certain events (such as death or development of a disease) over the simulation period. This kind of model usually uses probabilistic rather than deterministic techniques. Since microsimulation models are based on individual data, they may avoid bias due to aggregation. Also, since they work on individual data, they can easily incorporate many risk factors, and outcomes can be easily broken down according to specification of individuals. However, despite their richness, these models have encountered criticism

because of their complexity. Furthermore, development and maintenance of these models can be costly in terms of time and money[217].

Cell-based models (IMPACT[4], PREVENT[225]) are widely used in decision-making. Their growing popularity can probably be attributed to increases in computer literacy and computer power, plus easier access to organizational data[226].

Cell-based models vary widely in size and complexity. To construct a cell-based model, a population can be divided into subgroups, for instance, by age, sex, treatment and risk factor exposure. It is assumed that all the individuals within any given subgroup are similar if not identical. The probability (or rate) of an event occurring during a specified time period is applied to the specific subgroup. The estimated events for each of the categories are then summed to produce outcomes for the whole population.

Cell-based models can have considerable detail on the population; for instance, sometimes projections can be based on age-sex-race or marital status groups. However, these models do not typically include individual-based longitudinal information, and their estimations are aggregated[226].

Cell-based models have several potential advantages compared to other model types:

- Spreadsheet software is widely available
- Depending on the complexity, the time, cost of building and maintaining it is usually less expensive than microsimulation approaches
- While some require extensive training, most are relatively simple and user-friendly
- Many are very accessible; however, detailed assumptions should ideally be available for review[226].

These models also have some limitations:

- Spreadsheets may include erroneous formulae, incorrect ranges, omitted factors, data input errors, incorrect use of built in functions and duplication of effort[226;227]
- With addition of new variables, the number of cells can become unmanageable

Model classifications are not mutually exclusive; therefore a model can belong to more than one category.

1.5 The steps involved in developing a model

There are important steps to consider in developing a model[217]:

1.5.1 Problem definition

The question that the model is to answer must be explicitly defined before starting to build it. The disease(s) or outcome(s) being modelled, interventions under consideration and the population should all be specified. The problem would usually have a clinical relevance, and cause and effect relation should usually be well established[220].

1.5.2 Model specification

The choice of model will influence the assumptions that need to be made and which will therefore impact on the output. Microsimulation approaches provide flexibility but may require technical experts to help develop and interpret them. Cell-based models are simpler but generally provide aggregate estimates of outcome[217]. However, they can be useful in determining population impact of an intervention.

It is important that models are developed co-operatively with epidemiologists and clinicians. In particular, the researchers must decide whether to include the prevalent population and/or incident population, and how to determine the base scenario against which to compare other scenarios[217].

1.5.3 Data gathering and incorporating

Once the type of model is decided, the type of outcome parameters must then be determined and estimates of event probabilities obtained or developed.

Deaths prevented can provide useful information but can be relatively limited since it does not consider the length and the quality of that life[217]. In the evaluation of health care interventions a commonly used outcome is life-years-gained (LYG). In this process the intervention that maximizes life expectancy will be identified. However LYG does not take account of the quality of life. Quality adjusted life years (QALY) are therefore another useful measure of effectiveness and has the advantage of unifying mortality and morbidity in one measure[217]. Disability adjusted life years (DALYs), an internationally standardised form of QALY, have been used widely in the WHO Global Burden of Disease Project. DALY expresses years of life lost to premature death and years lived

with disability of specified severity and duration. One DALY is thus one lost year of healthy life[228].

What type of data should be used in the models?

Models require considerable data input and data sources need to be recent and credible. However, the availability of comprehensive high quality data remains a problem.

The data may come from a variety of sources including clinical trials, meta-analyses, surveys, databases, medical records, audits, Delphi panels (expert opinion) and official tariff lists for health care resource use[229].

Clinical trials produce the best evidence of efficacy of an intervention. However, since their study groups are restricted with inclusion and exclusion criteria, generalisation is always an issue so that the outcomes may not reflect the usual practice[220;229;230].

Meta-analyses may be a good source of efficacy data, if the outcomes are potentially generalisable to the target population. However, they are often subject to certain biases either from studies available (publication bias) or from the selection of studies for the analysis (inclusion bias; if criteria are chosen to produce intended results). The method of meta-analysis is also important. If there is significant heterogeneity, the results should usually not be combined[220].

Expert opinion can be a useful source when there is no published or reliable information on a particular area[229]. General practitioners or specialists can provide information based on their own experience on compliance or treatment uptake. However, such opinions can be subjective, and will differ between experts. Therefore a representative sample of the actual practicing physicians is generally desirable[220;229].

Surveys and observational studies can provide vital prevalence data for the models. However, their main objective may be different so that they can provide only limited detail on certain variables. Cohort studies and repeated cross-sectional studies can provide valuable and relatively unbiased information on the natural history of a disease and risk factors and lag times[220;229].

Official statistics are often very useful sources for population and mortality information. However, depending on the practice, they can be subject to reporting and

coding inaccuracy. Furthermore, in some countries their precision and ease of access can be questionable [220].

The data sources used in modelling should therefore be explained in adequate detail. The selection criteria for studies and data sources should be described and the strengths, weaknesses and possible sources of bias should be discussed[220].

All models therefore need to be validated and subjected to sensitivity analysis to identify the impact of different parameters[217].

1.5.4 Sensitivity analysis

In modelling studies uncertainty in data is a particularly problematic area. Sensitivity analyses should therefore be employed to quantify this uncertainty. There are different types of sensitivity analyses. The most common form is **simple sensitivity analysis,** where one or more parameters of an evaluation are varied across a plausible range[231]. If only one parameter is changed at a time while the others retain their base-case specifications, it is called ***'one-way sensitivity analysis'***. If more than one parameter is changed at the same time then it is called ***'multiway-sensitivity analysis'***. Any confidence intervals presented for the estimations can usually be included into sensitivity analyses. Multiway sensitivity analysis can take the form of scenarios, which explore the implications of alternative 'states of the conditions'[231].

Threshold analysis is concerned with identifying the critical value of parameters above or below which the conclusion of a study will change[232]. It can produce a useful graphical presentation, and is quite helpful when a parameter in the model is continuous and indeterminate. This approach is most often used in cost effectiveness analyses.

The Analysis of Extremes Method involves incorporating the best and worst estimates of inputs, and then generating extreme estimates for output. This kind of sensitivity analysis can be very efficient in dealing with uncertainties in data input. However, this method does not usually provide information about the likelihood of these 'best' or 'worst' scenarios. In most cases, the probability that all the worst cases or good cases occur simultaneously is small[231].

Probabilistic sensitivity analysis is more complex than the analysis of extremes, but it usefully allows the modeller to assign ranges, distributions and probabilities to uncertain variables[231].

1.6 Assessing model quality

When assessing the quality of a model, one should consider the system being modelled, the elements included and excluded, the model structure, the risk factors and the probable effects of known trends and the model assumptions-stated and unstated[217]. In the ISPOR Task Force Report, Weinstein et al[216] recommended three dimensions: Model structure, data and validity:

1.6.1 Model structure

The model should be structured to ensure its inputs and outputs are relevant to the decision making process. The health states defined in the model should correspond to the natural history of the disease. The structure of the model should be consistent with the theory of the health condition and with the available evidence on causal relationships between variables. The structure of the model should be as simple as possible while capturing the underlying essentials of the disease process and interventions. The description of the model should be sufficiently detailed so that the model can be replicated mathematically. The assumptions and input parameters, and the logic connecting them to outputs should all be stated clearly (Transparency).

The time horizon of the model should also be long enough to reflect the impact of the interventions[216].

1.6.2 Data

Systematic reviews of the literature should be conducted on key model variables. Where the data are not available or not reliable, assumptions have to be made and they can be tested with sensitivity analyses. All models should include extensive sensitivity analyses for key parameters. Ranges should accompany the estimates from the model. Data quality and availability should be evaluated and the inclusion or exclusion criteria should be defined for data sources[216].

Data modelling refers to the mathematical steps that are taken to transform empirical observations into a form that is useful for decision modelling. This involves methods of incorporating estimates of treatment effectiveness from randomised clinical trials, combining disease specific and all-cause mortality rates or risk factor prevalence and interventions. These should be defined in enough detail in the model.

1.6.3 Validation

In the ISPOR Task force report, the validation of models was grouped into three categories:

Internal validation

Models should only be used after careful testing to ensure that the mathematical calculations are accurate and consistent with the specifications of the model. This process can be done by using null or extreme input values and checking whether they produce the expected outputs[216]. Checking the model formulas, inputs and outputs by a second author may also help. The results of the model should make sense in terms of both the theoretical considerations, and also in intuitive terms (face validity) [216].

Models should be calibrated against the actual data when possible. However, calibration is possible only if inputs and outputs are available over the time frame being modelled.

Between model validation

Models can also be validated against each other (convergent validity)[216]. Models addressing the same problem would be expected to produce similar results with similar assumptions and input parameters (corroboration).

External validation

Models should be based on best available evidence at the time that they were built. Model outputs or estimates should be consistent with the observed data. Tests of predictive validity - the ability of the model to make accurate predictions of future events- are valuable, but not essential. In some models splitting the data into two time-periods can be useful to check the predictive validity of a model[233]. For example data for years 1990-1996 are used to generate a regression model, which is then applied to

the 1997-1999 dataset, and used to predict outcome for 1997-1999 period. These predictions are then compared against the observed outcomes for 1997-1999. This method may provide information on model's validity for different datasets and periods. Models should never be considered as complete and unchangeable tools to predict future. They should be updated according to new evidence and scientific knowledge[216]. A model should not necessarily be criticized for failing to predict the future. However, it should be possible for a good model to be recalibrated or re-specified to adapt to new evidence as it becomes available[215].

EXISTING CHD HEALTH POLICY MODELS

The Global Burden of Disease model includes ten major risk factors for global disease burden. They are malnutrition, poor water quality, unsafe sex, alcohol, occupation, tobacco use, hypertension, physical inactivity, illicit use of drugs, and air pollution246. CHD is included in the model, and is modelled as being caused by tobacco use, hypertension and physical inactivity, and reduced by alcohol at all levels of consumption.

Models are being increasingly used in health policy decision-making. In terms of CHD health policy models a wide variety exist. Some CHD models consider risk factors alone[234], risk factors and cardiovascular treatments[4], secondary prevention such as cholesterol lowering treatment[235] or estimates of general practice workload[236]. Their quality and utility may vary. In this section, I will describe a systematic review in which I evaluated the strengths and limitations of existing CHD policy models.

1.7 Methods

For this systematic review, we defined a CHD policy model as a tool that may help to explain or predict the outcome of CHD interventions (specific treatment or cardiovascular risk factor change, or the implementation of a new strategy) at the population level.

Search strategy

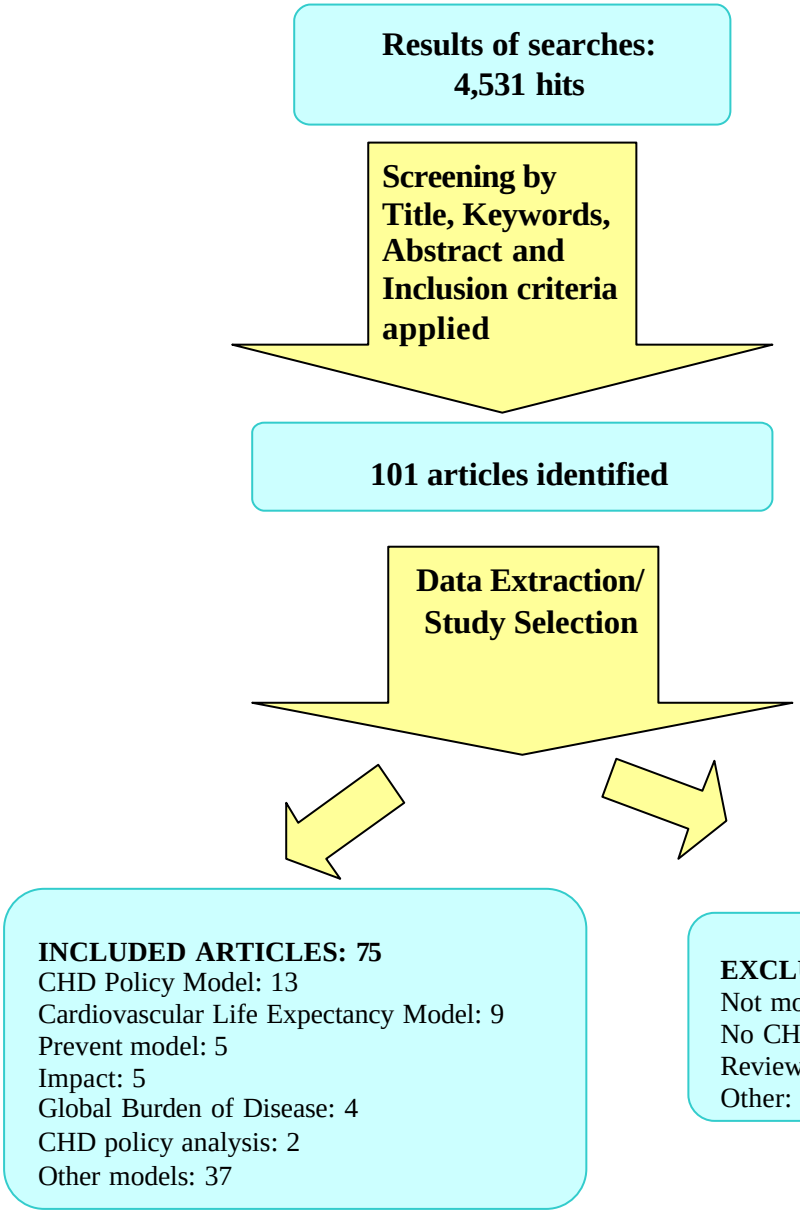
A search strategy was developed, piloted and run in MEDLINE and EMBASE electronic databases supplemented by screening reference lists of relevant articles and reviews. Electronic searching within the databases included 'coronary heart disease or synonyms' and 'model or synonyms' as key words. Both key words and MeSH headings were used *(Appendix 1).* The search strategy was validated using ten key papers already known to the authors; all ten papers were captured by the search strategy. The search identified 4,531 articles initially, and a further 17 were identified by checking the references. All the records were imported to 'Reference Manager'. By checking the titles and abstracts for the terms 'model', 'coronary heart disease' or 'population', the number of articles reduced to 275. Two independent reviewers (BU, SC) checked the titles and abstracts of all papers initially identified, and then screened

the articles for inclusion and appraisal. The two reviewers independently classified each article and agreement was good (Kappa = 0.76).

Inclusion and exclusion criteria

Any CHD modelling study was included if it reported on a key outcome (deaths prevented, life years gained, prevention cost, treatment cost, mortality, prevalence, incidence or disability) in a defined population. Models simply describing animals, cell lines, clinical series, cohorts or estimates of individual risk were excluded. *Figure 6.1* illustrates the flowchart for the search and review process. Excluded articles are listed in Appendix 4. In total, 75 articles were critically appraised and 26 articles were excluded.

Figure 0.1 Flowchart of search strategy for CHD policy models



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Data extraction and assessment of model quality

A pre-piloted form was used for data extraction *(Appendix 2)*. Articles were categorised according to the specific models that they described. Each paper was then critically appraised using explicit quality criteria. There are no universally accepted lists of appropriate quality criteria for model papers. However reviews by Weinstein215, and Edwards226, and recent guidelines International Society for Pharmacoeconomics and Outcomes Research (ISPOR)216 have suggested useful quality criteria. Using these sources215;216;226, we created a grading system, based on sensitivity, validity and transparency of the model *(Appendix 4)*.

Scoring system

Papers were graded on the basis of whether a sensitivity analysis carried out, the validity was checked, data quality presented, illustrative examples were provided, assumptions stated, if model was potentially available to the reader and if potential limitations such as assumptions, confounding, lag times and competing causes were discussed. A simple scoring system was developed, with maximum of ten points available. A point was awarded for each key feature listed above. Each paper was scored and given an overall grading as methodologically 'poor= overall score 0-3', 'adequate=4-7' or 'good=8-10' on an a priori basis.

1.8 Results

A total of 75 articles describing 42 different CHD policy models were finally included from 4,531 initial papers *(Figure 6.1)*. Due to space restriction, we presented here summaries of the six principal CHD policy models used to address several health policy questions, all based on large populations, and all with more than one publication *(Table 6.1* and *6.2)*. Critical appraisals of each paper are provided in *Appendix 4*.

Papers excluded from the review

Papers excluded and the reasons for exclusion are listed alphabetically in the *Appendix 4, Table 8*. The main reasons for exclusion were that the paper was not a modelling study, it did not report on CDH outcomes, or it was only a review paper.

Model methodology and structure

Model methodology varied widely. 12 (29%) of the 42 models were microsimulation or state transition Markov models, eight (19%) were cell based spread sheets, eight (19%) were life table analyses, four (9%) used Monte Carlo simulation techniques, four (9%) used logistic or linear risk functions, three (7%) used population attributable risk fraction estimations and three (7%) used a variety of other methods such as decision analysis *(Appendix 4)*.

Box 0.1 Summary of structures and methodology used in the six major models

The Coronary Heart Disease Policy (CHDP) Model was developed in 1980s as a state-transition, cell based model[222]. It was used to examine trends in CHD mortality[233;237] and expected gains in life expectancy from risk factor modifications[238]. This model was also used to evaluate the cost effectiveness of medical interventions for primary and secondary prevention of CHD[239-242] and health promotion activities[243].

The model was based on the 1980 US population and mortality statistics. It consists of three sub-models:

- A *demographical/ epidemiological* model, which represents the disease-free population aged 35-84 years. Here the population is stratified by sex, age groups and cardiovascular risk factors. This model includes risk factors as categorical variables, therefore in total over 5,000 cells are required. It then uses a logistic risk function based on the Framingham equation to calculate the annual incidence rates of CHD events for each cohort.
- A *bridge* model, which covers subjects for the first 30 days after they develop coronary disease. Using a CHD incidence data from Minnesota, the model initially determines whether the first event is angina, myocardial infarction or cardiac arrest[222].
- A *disease history model*, which includes the survivors after the first 30 days, places them in 12 CHD states by age and sex, and then follows them through treatment pathways.

This model allows the user to simulate the effects of an intervention (either risk factor modification, or therapeutic) by changing case fatality rates and observing the effect on

mortality, morbidity and costs for up to 30years.

CHD Policy Analysis Model, is a microsimulation model being developed for the Department of Health by the London School of Hygiene and Tropical Medicine and Universities of Southampton and Birmingham224;244. The primary prevention component of the model aims to simulate the impact of different primary prevention strategies on benefits and costs 244. The treatment component of the model evaluates the impact of different treatments given to different groups of CHD patients, commencing with stable angina224.

PREVENT is a cell based simulation model developed by Gunning-Schepers in the 1980s the Netherlands225. It can be used to estimate the health benefits of changes in population risk factor prevalence comparing i) continuation of existing trends with ii) alteration of the proportions of the population with given levels of risk factors. The model allows one risk factor to be associated with more than one disease and one disease to be associated with more than one risk factor. Demographic evolution is also taken into account in simulations225.

Cardiovascular Life Expectancy Model was developed by Grover et al (1992) in Canada to examine the cost-effectiveness of different treatment options for CHD234. The model includes primary and secondary prevention parts. The primary CHD part calculates the annual probability of dying from CHD or other causes and the annual risk of CHD events (with or without intervention) for a person without symptomatic CHD at entry to the model. The annual risk of developing specific CHD endpoints is based on data from the Framingham Heart Study.

After developing CHD, a person then moves to the secondary CHD model. This part calculates the risk of dying during the 12 months following a nonfatal myocardial infarction. The risk estimations are based on the Framingham logistic equations for primary events but after adjustment for the presence of CHD234.

The predicted annual cumulative mortality difference with and without the intervention over the remaining total life expectancy represents the total years of life saved after intervention.

The IMPACT CHD mortality model is a cell-based model originally developed by

Capewell and colleagues in 1996[4]. Using an MS EXCEL spreadsheet, this model combines data from many sources on patient numbers, treatment uptake, treatment effectiveness and risk factor trends to estimate the deaths ***prevented or postponed*** (DPPs) over a specified time period. It can therefore be used to estimate the proportion of a mortality decline over a certain time span that might be attributed to specific treatments or risk factor changes.

The Global Burden of Disease (GBD) model developed at WHO by Lopez and Murray, is an example of models which use population attributable risk percentage (PAR %) estimations. The model can calculate the attributable burden of disease for a specific risk factor, population and time, which is defined as 'the difference between currently observed burden and the burden that would be observed if past levels of exposure had been equal to a specific reference distribution of exposure'. The reference distribution of exposure is defined as the risk factor exposure with lowest relative risk[245;246].

The GBD Model has five components: causes of death, descriptive epidemiology of disabling sequel, burden attributed to selected risk factors, projections of burden for the future and sensitivity analyses. Cause of death data are obtained from vital registrations or other sources. Data on 107 disorders and selected disabling sequel were investigated regarding average age of onset, duration, incidence and prevalence. Burden of disease and injury attributable to ten major risk factors were calculated. The model uses attributable fractions, taken from reviews and meta-analyses, applied to the population of a region to calculate the burden of disease of these risk factors[246]. Burden of disease is measured using disability adjusted life years (DALYs) calculated as the sum of years lost and years lived with disability[228].

Comprehensiveness

Among the 42 models, 29 (69%) included only risk factors for primary prevention and 8 (19%) only considered treatments. Only 5 (12%) models included risk factors and treatments together. The CHD Policy and the IMPACT model were the most comprehensive since they both included a wide range of risk factors, CHD categories and effective treatments *(Box2)*. The CHD Policy Analysis Model represents a

derivative of the CHD Policy Model[244]. The CHD Policy Analysis Model eventually aims to include many treatment categories but has not been completed *(Box 2)*.

Box 0.2 CHD risk factors and treatment categories included in the six major models.

The Coronary Heart Disease Policy Model includes major risk factors such as smoking, total cholesterol, DBP and relative weight, which are necessary to estimate CHD risk using Framingham Equations. The model considers disease categories such as angina, AMI, sudden death, post MI, CABG, PTCA. Individual CHD treatments are also considered such as statins, aspirin, and beta-blockers in different publications based on this model.

The ***PREVENT*** Model is a primary prevention model and therefore only considers risk factors: smoking, cholesterol, hypertension, obesity, physical activity and alcohol use.

The Cardiovascular Life Expectancy Model estimates the annual risk of developing specific CHD endpoints based on data published from the Framingham Heart Study. It therefore includes risk factors of age, sex, diastolic blood pressure, total cholesterol, HDL cholesterol level, left ventricular hypertrophy, glucose intolerance and smoking status[247].

The CHD Policy Analysis Model resembles CHDP model by Weinstein et al. It has primary prevention and CHD treatment parts. The primary prevention component includes risk factors such as age, sex, systolic blood pressure, total cholesterol, and smoking[244]. The disease events included are stable angina, unstable angina, myocardial infarction, sudden cardiac death, stroke death, other cardiovascular death, cancer death and death from other known and unknown cause[244].

The IMPACT Model considers comprehensive risk factors and CHD categories and treatments. For primary prevention the model includes smoking, cholesterol, blood pressure deprivation, obesity, diabetes and physical activity. It also includes primary prevention with statin therapy.

The Disease categories (and treatments) (included: **AMI:** Cardiopulmonary resuscitation, thrombolysis, aspirin, PTCA, Beta blockers, ACE inhibitors); **Secondary prevention following MI, CABG or PTCA):** (Aspirin, Beta blockers, ACE inhibitors, Statins, Warfarin, Rehabilitation); **Chronic angina:** (CABG surgery, Angioplasty,

Aspirin, Statins); **Unstable angina:** (Aspirin, Aspirin & Heparin PG HB/HA inhibitors); **Heart failure:** (ACE inhibitors special lactose, aspirin, statins); **Hypertension treatments:** (All).

Model Population

Most (33, 79%) of the 42 models included this review considered specific populations, 4 (10%) and 5 (11%) of them were based on patients and hypothetical cohorts respectively.

Most of the models were restricted to young and middle-aged groups, generally 15 to 64 years *(Table1-7 in Appendix 4).* However the CHD Policy Model, IMPACT and CHD Policy Analysis Model considered groups aged up to 84 years. None of the models specifically considered non-Caucasian populations.

Model outcomes

Most common outcomes reported in the models were number of deaths prevented 25 (60%), 17 (41%) life years gained, 17 (41%) CHD incidence and 27 (64%) cost/cost effectiveness. Fewer papers reported on CHD deaths 10 (24%), CHD prevented 9 (21%), prevalence 6 (14%), QALY 6 (14%), DALY 4 (10%) admissions 3 (7%).

Model quality

Relatively few papers included in this review reported on model quality. Although sensitivity analyses were reported in 20 (48%) of the models, the majority were one-way rather than multi-way sensitivity analyses.

Validity of the model was assessed in 10 (24%) of the models. In the CHD Health Policy Model this was done by comparing the CHD deaths estimated by the model to the actual CHD deaths observed in 1990 using US vital statistics233. In the IMPACT Model, validity was likewise checked by comparing estimated fall in CHD deaths with observed fall4;248. Six other models also compared model estimates with observed figures125;223;249-252. In PREVENT, model validity was checked by comparing model estimates with another estimation method253. In the Cardiovascular Life Expectancy Model, predictive validity was checked by comparing the model estimates

with events observed in primary and secondary prevention trials254;255. Only two models (7%) reported on calibration of the model estimates against observed data. CHD Health Policy model was calibrated using life years estimated from the model compared with life expectancy from 1980 national statistics238. Kottke's model used actual mortality rates from the North Karelia cohort for calibration256. Only two of the models had been replicated in different populations (PREVENT257;258 and IMPACT5).

On *Table 6.2* quality evaluation of six major models were presented in detail. CHD Policy Model and IMPACT Model appeared to be better in reporting the model quality compared with the others.

Transparency and Limitations of the Models

Most models (36, 86%) explicitly stated their key assumptions. Illustrations or examples for estimations were provided in 14 (33%). Working versions of the models were potentially available in only (4, 10%). However, barely one fifth of the models reported on limitations of the models such as competing causes 8 (19%), lag times 7 (17%) or confounding 8 (19%).

The majority of the model papers received intermediate scores of 4-7 points *(Appendix3)*.

Table 1 Existing CHD Policy Models

Name of the model	Type of model	Model setting & Study population(s)	Risk factors included	Disease groups & treatments included	Outcomes	Sensitivity analysis	Validation	Strengths and limitations
CHD Policy Model (Weinstein and Goldman)	State transition Markov Model	USA, Men and Women aged 35-84	Smoking, total cholesterol, DBP and weight to estimate CHD risk using Framingham Equations	Angina, AMI, sudden death, post MI, CABG, PTCA Individual CHD treatments were considered in different studies such as statins, aspirin, beta-blockers etc	Number of deaths prevented, LYG, CHD incidence (number of arrests, angina, AMI), CHD prevalence, CHD mortality, cost per life year	In the initial model none. Subsequently papers reported one way sensitivity analysis	Model was calibrated using 1986 mortality data. Validity: model Estimates were compared with 1990 observed-92-98% fit reported.	First policy model rather basic. Steadily refined since then. Many papers in high impact journals
PREVENT (Gunning-Scheppers)	Cell based	Netherlands;Denmark, England Depending on the purpose aged <65	Smoking, cholesterol, hypertension, obesity, physical activity, alcohol	None	Number of deaths prevented, life years gained	One way, different scenarios	Not checked	Mainly a primary prevention model. Developed and adopted in many different populations.
CHD Life Expectancy Model (Grover et al)	Life table analysis, Cost-effectiveness model	Canada, Adult men and women, age group not clear	Smoking, total cholesterol, DBP, glucose intolerance, age	Did not consider CHD disease categories but treatments can be considered for primary prevention None ?	Years of life saved, cost per life year saved, years of life without CHD symptoms	One-way	Calibrated	This model uses hypothetical cohorts of participants. In most of the papers, time and the specific population are not clear.
CHD Policy Analysis (Sanderson and Davies)	Micro simulation	England and Wales, Up to 85 years. Men and women	Smoking, cholesterol, systolic blood pressure	Angina (stable-unstable), AMI, postMI, CABG, PTCA None - ?	Deaths prevented, morbidity prevented, CHD & noncardiac deaths, unstable angina		No validation reported	Future model may include secondary prevention treatments. NO sensitivity analyses. Model fit appears better for men

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Name of the model	Type of model	Model setting & Study population(s)	Risk factors included	Disease groups & treatments included	Outcomes	Sensitivity analysis	Validation	Strengths and limitations
					admissions, investigations, angiograms, PTCA, CABG			than women.
IMPACT (Capewell, Critchley and Unal)	Spread-sheet	Scotland, England &Wales, New Zealand, and, Initially M-F aged 45-84. IMPACT Model for England and Wales includes M-F 25-84	Initially smoking, cholesterol, blood pressure deprivation- then obesity, also diabetes and physical activity	This model is comprehensive and considers Vine CHD categories and over 20 specific CHD treatments	Deaths prevented or postponed, life years gained.	Multi way sensitivity analysis using Analysis of extremes	Estimated falls in CHD mortality were compared with observed falls	Considers all major effective treatments available for CHD and all major risk factors. Data quality adequate, used trial and meta-analyses: National population statistics and results from representative studies
Global Burden of Disease **Murray & Lopez**	Population Attributable Parish method	World divided into eight geographic regions M-F all ages	Malnutrition, poor water, unsafe sex, alcohol, tobacco occupation, hypertension, physical activity, illicit drugs, and air pollution	None	Disability adjusted life years (DALYs)	Multi-way sensitivity analysis - discounting and age weighting	None	A comprehensive and global model for WHO strategies. Well documented and described. CHD is included, and modelled as caused by tobacco use, hypertension and physical inactivity, and reduced by alcohol. Data quality: Extremely variable depending on the region

*** Abbreviations:** AMI- acute myocardial infarction, CABG- Coronary artery bypass graft, MI- Myocardial infarction, LYG - Life years gained, PTCA- Percutaneous transluminal coronary angioplasty

Table 2 Quality assessment for major CHD policy models

	Model Structure					Data Quality				Validation			Total
	Natural history of disease	Sufficient description	Assumptions	Inputs	Outputs	Inclusion criteria	Exclusion criteria	Data sources defined	Sensitiviy analyses carried out	Internal	External	Corroboration	
CHD Policy Model	3	3	3	3	3	3	3	3	3	3	2	2	**34**
PREVENT	1	3	3	2	3	3	3	3	2	1	1	1	**26**
CHD Life Expectancy Model	2	2	3	2	2	2	2	2	1	3	3	0	**24**
CHD Policy Analysis	3	3	2	3	3	2	2	3	0	2	2	0	**25**
IMPACT	3	3	3	3	3	3	3	3	3	3	1	2	**33**
Global Burden of Disease	2	3	3	3	3	3	3	3	2	3	0	0	**28**

Appraisal criteria: The elements of the model assessment were listed in table. A general opinion was developed after reviewing all the papers published from that individual model. Each one of the criteria was scored on a 0 to 3 point scale. 0: not reported/ not done, 1: reported superficially/done simply 2:reported with detail 3: discussed

1.9 Interpretation

This is the first comprehensive systematic review of CHD policy models. Previous reviews were restricted to a particular type[259-261] or particular application[261]. The increasingly wide use of modelling has thus far resulted in few attempts to evaluate model quality. We therefore aimed to systematically assess the quality of the modelling methodology rather than simply report on the reported results. A wide variety of CHD policy models have been developed with over 70 publications now available. CHD models have become more complex and comprehensive as a result of improving computer technology and wider usage[3]. In general, the quality of the models has also improved over time so that more recent papers tend to explicitly report on sensitivity analyses and assumptions and limitations.

Quality assessment of publications, is well described especially for randomised controlled studies[262]. However, there are no widely accepted quality criteria for modelling papers in general nor specifically for CHD policy models. We therefore developed simple evaluation criteria based on sensitivity analyses, validity, and these comprehensive reporting of assumptions and limitations. These criteria explicitly reflect the main quality components suggested in the recent ISPOR Guideline[216].

Models can allow a large amount of evidence to be considered simultaneously, by combining and integrating into a coherent whole different types of data from controlled trials, routine surveillance and expert consensus[3]. Models have been extensively used in policy making and resource allocation, since they permit policy makers to examine future options, or to simulate the effects of different scenarios within a population[217]. However, improved technology potentially allows both practitioners and policy-makers to use these models without necessarily understanding the inherent assumptions or data limitations [3].

Models require considerable data input and data sources need to be appropriate and credible. However, the availability of comprehensive high quality data remains a problem. The data may come from a variety of sources including clinical trials, meta-analyses, surveys, databases, medical records, audits, Delphi panels (expert opinion), routine statistics and official tariff lists for health care resource use[229]. Every modelling paper should therefore explicitly report and discuss data quality

methodological limitations and assumptions to address these discrepancies. However, few of the papers reviewed here critically evaluated their data quality.

Uncertainties about data are a perennial problem in modelling studies. Sensitivity analyses should therefore be employed to quantify the degree of uncertainty. In general, CHD models have only recently started to report sensitivity analyses[233;255;263].The most common approach is where one or more parameters of an evaluation are varied across a plausible range[231]. Confidence intervals can also be easily included in sensitivity analyses. ***One-way sensitivity analysis*** (where only one parameter is changed at a time while the others retain their base-case specifications) is obviously less rigorous than ***multiway-sensitivity analysis*** (where more than one parameter is changed at the same time). However, multiway sensitivity analyses remain uncommon[3;4;248;264].

Many of the papers reviewed here failed to provide sufficient detail to allow thorough evaluation. When assessing the quality of a model, one should ideally consider the system being modelled, the elements included and excluded, the model structure, the probable effects of existing trends in mortality and risk factors and the model assumptions- both stated and unstated[216;217] . The description of the model should be sufficiently detailed so that the model can be replicated mathematically.

In conclusion, CHD models offer a potentially valuable tool for policy development. However, existing models vary widely in their depth, breadth and quality. Few models have been calibrated, replicated or validated against a gold standard. Before being accepted as a policy aid, any model should explicitly include a statement of its aims, assumptions, strengths, outputs and limitations.

AN EVALUATION OF UK DATA SOURCES FOR CHD

1.10 Introduction

Chapter 4 described the massive burden of disease generated by CHD in the UK, and also raised potential concerns about the quality of the data describing CHD. This chapter will therefore focus on CHD data quality in the UK.

Policy decisions on health and health care require good evidence, particularly since resources are limited[3]. Good evidence to describe the current situation means not just information on the effectiveness of interventions, but also valid and reliable data on the disease burden and the provision of health care.

Modelling studies can provide decision makers with good evidence based results and they are based on data availability and quality[3]. In my thesis I will use IMPACT CHD Mortality model to explore recent CHD mortality trends in England and Wales. I therefore decided to evaluate the availability and quality of UK CHD data sources since 1981. I considered all 'public health' information sources for CHD, as defined in the recent 'Department of Health CHD Information Strategy'[265]. This included information on patterns of mortality and morbidity (including hospital admissions and episodes) and major cardiovascular risk factors by age, sex, and ethnicity.

1.11 Methods

UK data sources on CHD were initially identified and categorised according to the IMPACT CHD mortality model, which aims to explore CHD mortality trends in England and Wales during 1981-2000[248].

To build the IMPACT Model, information was required on a) population based mortality rates and patient numbers with different categories of CHD -acute myocardial infarction, unstable and chronic angina, heart failure, hypertension, CABG surgery and angioplasty; b) uptake of specific medical and surgical treatments; c) effectiveness of specific cardiological treatments and risk factor reductions and d) population trends in major cardiovascular risk factors (smoking, cholesterol, hypertension, obesity, diabetes, physical activity and deprivation)[248].

SEARCH STRATEGY

Potential data sources were identified and obtained by various methods including comprehensive electronic searches using keywords and MeSH headings. Databases searched included MEDLINE, EMBASE and DISSERTATION ABSTRACTS. This search was further supplemented by cross-checking reference lists of the key articles retrieved during the electronic search. I also examined conference proceedings, audit reports, relevant official web sites and personal correspondence *(Appendix 5).*

The main data sources for population and patient data were the Office for National Statistics (ONS)[266] and the British Heart Foundation's Annual CHD Statistics[2]. Information on treatment prescription and uptake were obtained from various national and local clinical audits[267-269] and surveys [157;201;270;271]. Data on efficacy of interventions and risk factor changes were reviewed from published randomised controlled trials, meta-analyses and population studies.

The British Regional Heart Study[272], General Household Survey[273], and Health Survey for England[48] were the main data sources for risk factor data.

Each data source was evaluated in terms of the following criteria: coverage and completeness (population of interest), coding accuracy (where these are reported in the primary data source), validity (the degree to which a variable measures what it purports to measure[274]- where this is reported in the primary data source) and generalisability (critical appraisal of the studies for their methodology), ease of access (availability of information either published or electronically), and inclusion of information on age and sex breakdowns, ethnic and socio-economic categories.

1.12 Results

Population and patient data sources

The main data sources for population and patient data are presented in *Table 7.1.* Data from ONS official statistics[195;266] were easily accessible both electronically and in published form. However Official statistics are not based on autopsies, therefore may over estimate CHD deaths in the elderly. The British Heart Foundation provided another useful source of annually updated CHD statistics for the UK[2]. The source includes data on CHD morbidity, mortality, prevalence, incidence and cost in the UK.

Information on patient numbers undergoing CABG surgery has been available from the United Kingdom Cardiac Surgical Register since 1977[197]. The register was based on voluntary and anonymous reporting of activity and hospital mortality for CABG, valvular and congenital heart disease surgical procedures performed in NHS Hospitals. Each unit was asked to return a standard questionnaire annually to the Society of Cardiothoracic Surgeons[197]. These data were then analysed and published as annual reports. However while reasonably complete, the Register lacks details on age, sex, ethnicity, social status and long-term survival.

Angioplasty patient numbers have been available from the British Cardiovascular Intervention Society's Audit returns since 1989[198]. These referred to angioplasty activity in all interventional centres in the UK, both NHS and private. The data had details on procedures and success, but lacked details on age, sex and other individual specific information.

The number of **acute myocardial infarction, angina** and **heart failure** admissions to hospitals was available from Hospital Episode Statistics (HES)[196]. HES provided information on in-patient care delivered by NHS hospitals in England since 1989. HES collected almost 12 million records per year, and each record contained over 50 items of information. Since these records related to named individuals, it was not possible to access them directly. The database contained information on diagnoses, operations, admission method, patients' age, sex and ethnic group, length of stay, waiting time, maternity care, psychiatric care, Healthcare Resource Groups (HRGs), NHS Trusts and Health Authority areas[196].

HES records described *episodes* of continuous in-patient care under the same consultant[196]. In cases where responsibility for a patient's care transferred to a subsequent consultant, there would be two or more records for the same patient. In 1999-2000, approximately 8% of admissions fell into this category[196]. HES could not provide details of the drugs used in hospitals, nor information concerning outpatients or patients treated in accident and emergency departments and then discharged home immediately. Another major limitation of the database was being unable to distinguish between first admissions and readmissions.

The number of **angina patients in the community** could be estimated using prevalence of 'ever experienced angina', available from the Health Survey for England(HSE) '98[48].

This was a series of annual surveys about the health of people in England carried out since 1991. The HSE contained a 'core', which was repeated each year, and each survey year has one or more modules on subjects of special interest. The HSE 1993, 1994 and 1998 had CVD modules and could therefore provide useful information on CHD, stroke, hypertension and other cardiovascular risk factors.

In the HSE, angina prevalence was measured as 'self reported angina'. In addition to this, the Rose questionnaire on angina and heart attack48 was used as an alternative estimation method. Overall angina prevalence was lower with Rose Questionnaire (2.6% in men and 3.1% in women) than that based on self-reported 'doctor-diagnosed' angina (5.3% and 3.9%). This suggests a possible overestimation in angina prevalence with self reported angina. However, Rose Questionnaire measures current angina rather than ever-experienced angina and prevalence of self reported 'current angina' was closer to prevalence measured by Rose questionnaire (3.2% and 2.5% in men and women)48. Angina patient numbers based on GP consultation rates could be expected to be substantially smaller than these prevalence based estimations204.

The population surveyed in HSE has been the population living in private households. Those living in institutions have not been covered. They are likely to be older and, on average, in poorer health than those in private households. Furthermore, a response rate for the survey varied substantially by survey year but was generally low. Interviews were carried out on 69% of individuals targeted, 58% had their blood pressure measured and only 47% gave a blood sample48.

The number of heart failure patients in the community was estimated using prevalence of 'treated heart failure' from Key Health Statistics from General Practice, 1998201. This report gave the prevalence of various morbidities and treatment data derived from general practitioner records and it provided data for age-sex groups.

Since this source was based on general practitioner consultations, it omitted those symptomatic subjects who did not present to the NHS, but who were detected by epidemiological surveys275;276. Furthermore, there is evidence of substantial limitations in coding accuracy and appropriate treatment of the condition175. Therefore, the actual number of heart failure patients in the community may be slightly higher than the estimated numbers using prevalence data from Key Health Statistics from General Practice [175].

Table 1 Population and patient data sources of information on CHD in the UK, 1981-2000.

Information	Source	Evaluation
Population statistics (1981-2000) (number) **Deaths by age and sex (1981-2000) (number)**	Office for National Statistics[195] Available online from Office for National Statistics [266] and as published reports [277]	Easily accessible, accurate and up-to-date Death certification complete standardised coding. Only minority based on autopsy. May over estimate CHD deaths in elderly.
CHD Mortality (rates)	Available as mortality statistics from Office for National Statistics [277;278] and from British Heart Foundation Annual CHD Statistics online or published reports [2]	Little information on ethnic minority or socio-economic difference.
CABG surgery patients (number)	CABG numbers from 1991-2000 available online on UK Society for Cardiothoracic Surgeons of Great Britain and Ireland's web site (http://www.scts.org/doc/2102)[197]. To obtain figures for England and Wales CABG numbers for Scotland and Ireland deducted from UK's figures.	Appear accurate. Lack detail on age, sex, ethnic group, social status and long-term survival.
Angioplasty patients (number)	Angioplasty numbers for 1991-2000 available online on British Cardiovascular Intervention Society's web site http://www.bcis.org.uk/audit/Bcis00.ppt[198].	Age and sex split not provided.
Angina patients admitted to hospital (number)	Number of angina patients admitted to hospital available from Hospital Episode Statistics 1999-2000 (http://www.doh.gov.uk/hes/index.html)[196].	Episodes not individuals. Coding accuracy improving. Lack detail of subgroups. No data on therapy.
Angina patients in the community (number)	Prevalence of 'ever experienced angina' is available from Health Survey for England 1998[48], and British Regional Heart Study[279].	Only prevalence not incidence.
Heart failure patients admitted to hospital (number)	Number of angina patients who admitted to hospital was available from Hospital Episode Statistics 1999-2000 (http://www.doh.gov.uk/hes/index.html)[196]	As for angina admissions.
Heart failure patients in the community (number)	Prevalence of treated heart failure patients in the community available from Key Health Statistics from General Practice 1998 report[201]	GP consultations; therefore omits subjects not presenting to NHS.

Cardiological treatments

Data sources on cardiological treatments in primary and secondary level are presented in *Table 7.2.*

The precise number of CHD patients who had cardio-pulmonary resuscitation (CPR) in the community (before reaching hospital) was not known, neither was the number of CHD patients who had CPR in hospital. These two figures could only be estimated from various surveys[157;280;281].

Information about **hospital admissions** in 2000 was available online from HES[196]. However, trend data, and details of hospital interventions were very limited.

Treatment uptake data were not available routinely, and came principally from isolated surveys and registers. For **treatment at the primary care level**, limited prescription and uptake data were available from the Prescribing Analysis and Cost Tabulate (PACT)[282], and a few published local audits and studies[166;283-287]. Broadly consistent uptake levels were reported for treatments in primary care settings in two different surveys[288;289]. The EUROASPIRE II Study provided treatment levels for the secondary care of CHD from a small number of selected UK hospitals, but age and sex breakdowns were not generally available[269]. Furthermore, generalisability of EUROASPIRE II results to whole UK practices is questionable.

Table 0.2 Data sources on CHD treatments in primary care and secondary care in the UK, 1981-2000.

Information	Source	Quality & Comments
Initial Treatments For Acute Myocardial Infarction		
Community CPR	Estimated using data from UK Heart Attack Study[157] and Scottish Heartstart[290]. Number of myocardial infarction admissions to hospital obtained from HES.	Ad hoc surveys and ambulance data only.
Hospital CPR	Number of hospital CPR patients estimated using 2000 HES data. Approximately 11 % of the patients admitted to hospital need CPR (The United Kingdom Heart Attack Study Collaborative Group[271] and BRESUS Study[280])	Isolated surveys only.
Thrombolysis **Aspirin** **Beta-blocker** **ACE inhibitor**	The United Kingdom Heart Attack Study Collaborative Group[271], Nottingham Heart Attack Register[269;291]	Isolated surveys, plus some data on numbers given thrombolysis. Routine information on hospital treatments for acute myocardial infarction not available.
Secondary Prevention Following Acute Myocardial Infarction, CABG Surgery or PTCA		
Aspirin Beta-blocker ACE inhibitor Statins Warfarin Rehabilitation including exercise	Limited data on secondary prevention from General Practice Research Database report[289] and EUROASPIRE II Study[269]	Isolated surveys[288] and a few ad-hoc audits only.
Unstable Angina in Hospital admissions	No routine data on therapy	No routine data.
Aspirin for Community Angina	Data mainly from a General Practice Research Database report[289]	Isolated surveys only.
Heart failure treatment in hospital	-	Isolated audits only.
Heart failure treatment in the community	Key Health Statistics From General Practice 1998[201]	Isolated papers.
Treatment of individual patients for hypertension	British Regional Heart Study[292] Caerphilly papers[293] and the Health Survey for England 1998[48]	Information limited especially in elderly.

Cardiovascular risk factor data sources

Population based cardiovascular risk factor data sources and their evaluations are presented in *Table7.3.*

The risk factors considered were blood pressure, smoking, total cholesterol levels, obesity, physical activity, diabetes, and deprivation. Population based risk factor data were available mainly from the British Regional Heart Study[272;292;294], the General Household Survey[273], and the Health Survey for England[48]. Information was very limited for the 1980s, but more extensive by the year 2000.

Blood pressure data were relatively limited until recently. The British Regional Heart Study provided some blood pressure data in 1981, but only for men aged 40-59[272]. The Dietary and Nutritional Survey of British Adults[295] reported blood pressure data from 1990 onwards and provided sex and limited age breakdowns (up to 65). The Health Survey for England has included blood pressure data since 1993[296].

Smoking prevalence was the exception among the cardiovascular risk factors with good data on trends easily available from successive General Household Surveys[200;273]. Age, sex and socio-economic status breakdowns were also available.

Data on **cholesterol levels** were very limited during the 1980s[294]. The Health Survey For England included cholesterol levels from 1993. However, changing laboratory methods used between surveys made the interpretation of these recent trends difficult[48].

Blood samples were analysed by different laboratories in different Health Surveys. The Royal Victoria Infirmary laboratories in Newcastle upon Tyne analysed blood samples in 1991 to 1993 and 1998 Health Surveys. However, the laboratories of the West Middlesex University Hospital had undertaken analysis of blood samples collected in the 1994 to 1997 Health Surveys. Although they both used the same method (DAX Cholesterol Oxidase) in 1994 and 1998, the equipment used was different. Some caution is therefore necessary when interpreting these results[48].

Data on **obesity** (defined as BMI>30kg/m^2) were available from two Department of Health surveys in early 1980's[297], and also HSE[295]. However, data on other anthropometric measures such as waist-to-hip ratio, were not available in the early 1980's but only from more recent population surveys[48].

Some indirect evidence of a decline in **physical activity** (an increase in car journeys and decrease in miles walked) was available from the Department of Transport's Statistics for Great Britain[298]. However, no comprehensive population-based measures were available before the Allied Dunbar Survey in 1990[299]. The British Regional Heart Study provided physical activity data limited to men aged 40-59[53;300]. However, definitions of physical inactivity have varied in different surveys, so comparable trend information were not available.

There were some studies on **diabetes** starting from the 1970s mainly focusing on treatment efficacy (The United Kingdom Prospective Diabetes Study)[301] and mortality in diabetic patients (British Diabetic Association Cohort Study)[302]. However, early information on trends in diabetes prevalence was available only from one population survey in Poole commencing in 1983[303]. The Health Survey for England provided self reported information on diabetes prevalence since 1991[296]. Trends in general practice consultations between 1994 and 1998 are also now available from the General Practice Research Database[304].

Socio-economic information was available on household income, adjusted for tax and benefits, and housing tenure from various sources including Social Trends[305] and the General Household Survey [200;273]. However, because deprivation scores describe relative deprivation on the basis of cross-sectional data, trend data for deprivation scores have not been generated. Data on socio-economic characteristics defined the occupation of the head of household, equalised income and health authority area type was available from Health Survey for England.

The **Barker hypothesis** states that low birth weight is associated with increased rates of CHD in later life[87]. To estimate the impact of birth weight trends, population birth weight data is necessary. However birth weight data is routinely available only from 1950s[306]. Data on earlier years is only available from small population registries. In Hertfordshire, from 1911 to 1948 weight at birth and at age 1year were recorded routinely[307].

Table 0.3 Data sources on cardiovascular risk factors in the UK, 1981-2000.

Cardiovascular Risk factors	Source		Evaluation
Information	**Initial Year (1981)**	**Most Recent Year (2000)**	
Population blood pressure	The Dietary and Nutritional Survey of British Adults [295] and British Regional Heart Study [272]	Health Survey for England 1998 [48]	Blood pressure data very limited until recent times. For early years The Dietary and Nutritional Survey of British Adults and British Regional Heart Study (only for men) provided mean blood pressure levels. Health Survey for England included these data since 1993.
Smoking prevalence	General Household Survey 1980 [273]	General Household Survey 2000 [200]	Good data for trends in smoking prevalence easily available from General Household Surveys and British Household Panel Survey categorised by age and sex.
Cholesterol	British Regional Heart Study [272]	Cholesterol levels measured in Health Survey for England 1994 and 1998 [48]. MONICA Glasgow and Belfast trends 1985-1995 available for comparison [308].	Limited data available for the early 1980s. Changing laboratory methods used in the Health Survey for England (1994-1998) made interpretation of recent trends difficult, even when supported by trends from UK MONICA surveys .
Obesity	The Heights and Weights of Adults in Great Britain [297]	Health Survey for England 98 [48]	Data on obesity (defined BMI >30) available from two DoH surveys in early 1980s. Data on other anthropometrical measures i.e. waist to hip ratio, were not available in early 1980's but these data available from some more recent population surveys (Health Survey for England).
Physical activity	British Regional Heart Study [272]	Allied Dunbar Survey 1990 [299]	No comprehensive population-based measures were available before Allied Dunbar Survey 1990. British Regional Heart Study data limited to men aged 40-59. Definitions of physical inactivity varied in different surveys so comparable trend information not available directly. Some indirect evidence of a decline in physical activity available from Department for Transport's Transport Statistics for Great Britain report [298].
Diabetes	Poole Diabetes Study [303]	Health Survey for England 98 [48], General Practice Research Database [309]	Data on diabetes prevalence is either not available or not comparable for early 1980s. More recent trend information is available from Health Survey for England and General Practice Research Database [309] .
Deprivation	1981 Census data	2001 Census data awaited	Standardised trend data for deprivation score not available. Information available on: household income, adjusted for tax and benefits, housing tenure.

1.13 Interpretation

Information on CHD in the UK is frequently patchy, obsolete or simply not available. Although routinely collected data provide large quantities of health information, often covering the whole population over a long period of time, such sources have limitations and are underused[310]. The Office for National Statistics provides useful updated population and mortality statistics. Furthermore, much of the Office for National Statistics information is available electronically, which makes it much more accessible for users. Likewise Hospital Episode Statistics, which summarise admissions to the NHS hospitals, are also available electronically; however they lack detail on interventions at the hospital level. The British Heart Foundation's HEARTSTATS website is also developing rapidly, and provides an increasingly wide range of CHD statistics plus brief comments *(http://www.heartstats.org/homepage.asp).*

Public health information on CHD in the UK must be improved. At present, the NHS annually spends over £2 billion on a range of evidence-based initiatives for the treatment of CHD. However, evaluation of these initiatives using existing routine data is simply not possible. Furthermore, monitoring this common and devastating disease is almost confined to analysis of mortality statistics. Over 35,000 CABG operations are performed each year, however survival even two years later is not routinely available[311]. Thirty day case fatality following admission for AMI or CABG surgery have been used as Department of Health performance indicators[312]. However, variations in performance indicators between individual hospitals are vulnerable to differences in coding practices and case-mix[313].

Other Northern European countries have developed and implemented better CHD monitoring systems. The Information and Statistics Division (ISD) in Scotland collects good data on all patients treated for CHD and the procedures they receive. Scotland's routine NHS data is of high quality and data linkage allows the investigation of the epidemiology and treatment of heart disease across the population, with comprehensive analyses then being possible on different forms of the disease, including myocardial infarction and heart failure[123;144;192;313;314].

CHD mortality rates in Finland were once the highest in the world[315]. A series of regional risk factor surveys (FINRISK) have been carried out there every five years since the early 1970s[192;315;316]. These use a standardised methodology, include all the major CHD risk factors, with high participation rates and a large sample size (approximately 14,000 for the

2002 survey). Reliable estimates of trends and their contributions to CHD mortality declines can therefore be made over a 30-year period. They also allow relatively quick identification of adverse developments such as the increase in smoking among women observed in the 1980s to early 1990[317].

Monitoring of risk factors and of secular trends in risk factor epidemiology is also available in Norway[318]. Cardiovascular risk factor studies have been conducted in different regions since the late 1950s. Since the 1970s, the National Health Screening Service (SHUS) cardiovascular disease screening and prevention programmes visit all municipalities, every three years and achieve high response rates[318].

In the USA, the National Health and Nutrition Examination Survey (NHANES) has been periodically conducted since the early 1960s to obtain nationally representative information on health, nutritional status, risk factors and health behaviours in the population. NHANES III (1988-94) is the seventh of these[319] and data from NHANES 1999-2000 is currently available from (webpage: http://www.cdc.gov/nchs/data/nhanes/frequency/filelist%204-2003.pdf)

In England and Wales, the CHD NSF, NHS Plan and CHD Information Strategy all explicitly recognise the huge importance of disease monitoring and service evaluation. All have made a number of specific and sensible recommendations. However, at present over 99% of the £2 billion NHS CHD budget is spent on medical interventions, particularly revascularisation. Less than 1% is currently spent on the monitoring of CHD[2;265]. These are inadequate resources for even basic information strategy or technology. Furthermore, although some national datasets (such as the Health Survey for England) can support the Information Strategy, such datasets are not 'locally owned' and lack the scale to analyse specific local population groups, such as ethnic minorities[320].

In conclusion, future CHD disease monitoring and evaluation will require more comprehensive and accurate population-based information on trends in patient numbers, treatment uptake and risk factors. This will require adequate resources to improve existing information systems. Regular and comprehensive surveys (including women and elderly people), using standardised methodology will also be essential.

In terms of my thesis, these findings mean that all data, whether routine statistics or surveys have to be treated with some caution. The need for a sensitivity analysis will therefore be explicitly discussed in the next chapter.

Description of the IMPACT Model

In *Chapter 6*, I discussed the concept of modelling and reviewed some of the CHD models in use today. In this chapter, I will describe the IMPACT Model in detail and explain the methodology.

In 1996, Capewell et al. developed and refined IMPACT CHD mortality model[4]. Using an MS EXCEL spreadsheet, this cell-based CHD model combines data from many sources on patient numbers, treatment uptake, treatment effectiveness and risk factor trends to estimate the ***deaths prevented or postponed*** (DPPs) over a specified time period. It can therefore be used to estimate the proportion of a mortality decline over a certain time span that might be attributed to various risk factor changes or to specific treatments. For example, in Scotland CHD mortality declined by 29% between 1975 and 1994. Using the IMPACT model, it was possible to attribute approximately 40% of the fall to medical therapies and one third to the reduction in population levels of smoking[4].

The IMPACT model was validated against the actual mortality fall observed in Scotland[4], and then replicated in New Zealand[5]. It was then used to estimate how many additional deaths could potentially have been prevented by simply increasing the uptake of appropriate treatments by eligible patients[321] in Scotland in 1994 (approximately 4,000). The model was also used to estimate the additional deaths which might potentially be prevented in Scotland by further reductions in risk factors such as smoking, cholesterol and blood pressure[322].

In collaboration with the National Public Health Institute (KTL) in Helsinki, Finland, validation and development of the IMPACT model has recently been completed. This used high quality linked data on deaths and hospital activity, plus MONICA data on risk factors[192]. The findings suggested that cholesterol reductions were much more important in explaining trends in CHD mortality (1982-1997) in Finland compared with UK *(personal communication with Julia Critchley, 2003).*

The original IMPACT model was thus restricted to the Scottish population of 5.1 million. Furthermore it demonstrated a number of methodological limitations, including being restricted to 1994, considering only three risk factors and omitting modern therapies such as primary angioplasty for AMI, and PG IIb/IIIb antagonists for unstable angina. The aim of my PhD project was therefore to further develop the IMPACT Model methodology, update it and

apply it to the much larger and more complex England and Wales population[248]. I would then be in a position to examine LYGs, potential impact of improvements in uptake of treatments, or reductions in major risk factors, as well as mortality trends in England and Wales between 1981 and 2000.

1.14 Building an IMPACT Model for England and Wales

Selection of an appropriate population and time frame

The England and Wales population was chosen to examine recent CHD mortality trends because:

i) The National Service Framework for Coronary Heart Disease, published in 2000 highlighted an obvious need for such work to support the NSF and to evaluate its impact

ii) No comprehensive analysis of UK trends in CHD mortality, risk factors and treatments had been published

iii) Relatively extensive data were available for England and Wales describing the population, mortality trends and, to a lesser extent, morbidity trends

Age range

The model was initially built without an upper age limit. However, it became increasingly clear that data were sparse over the age of 85 years. Furthermore, there was some evidence that the accuracy of CHD on death certificates decreased in the elderly[183]. It was therefore decided to restrict the model to between ages 25 to 84 years.

The baseline (1981) and final years (2000) were chosen on the basis of several factors:

i) The total duration needed to be at least 10 years in order to cover a reasonable change in mortality rates.

ii) There needed to be adequate data on risk factors and treatments for the base year

iii) The final year needed to be as recent as possible to maximise its value to clinicians and policy makers.

After some pilot work, a **20-year period between 1981 and 2000** was chosen to model the mortality trends in England and Wales.

Refining and developing the IMPACT mortality model

The cell-based IMPACT mortality model was further developed and refined during my PhD studies. I added new treatments and new risk factors to the model. I also introduced new methods to quantify the cumulative effects of multi therapy in secondary prevention groups. The methodology sections will provide further detail around these issues. A list of these changes is presented below, and the approaches developed to address these issues are explained in the appropriate sections and boxes (flagged in italics).

Box 0.1 Principal changes and refinements made in English IMPACT Model

New treatments added to the IMPACT Model

- Primary angioplasty for AMI patients
- Platelet glycoprotein IIB/IIIA inhibitors for unstable angina
- Spironolactone, aspirin and statins for angina and heart failure patients
- Statins for primary prevention *(Box 8.9)*

– **New risk factors added to the IMPACT Model**

- Obesity
- Diabetes
- Physical activity
- Deprivation *(Page 99-100, Box 8.11)*

– **Mant and Hicks correction was applied for secondary prevention therapies** *(Box 8.3)*

– **New possible overlaps between patient groups considered** *(Box 8.4)*

– **Impact of risk factor changes in CHD patients was estimated** *(Appendix 9)*

The model was then revised to incorporate data for England and Wales. Data were identified and incorporated for men and women aged 25 to 84 years in England and Wales detailing;

a) CHD patient numbers,

b) uptake of specific medical and surgical treatments,

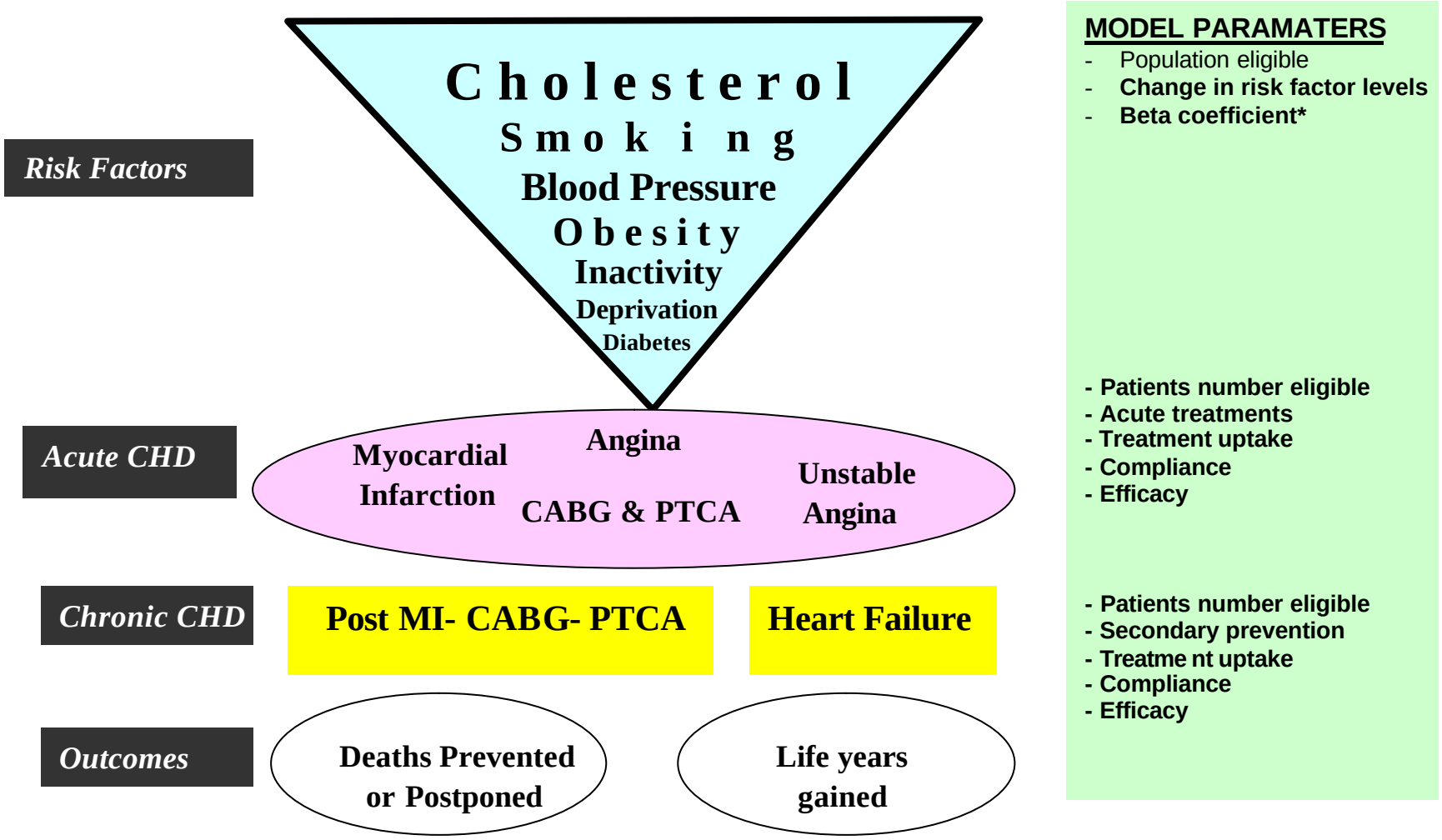
c) population trends in major cardiovascular risk factors (smoking, total cholesterol, hypertension, obesity, diabetes, physical activity and socio-economic deprivation),

d) effectiveness of specific cardiological treatments, and

e) relationship between specific risk factor reductions and CHD mortality.

A flowchart is presented to describe the IMPACT Mortality Model and parameters included in *Figure 8.1*.

Figure 0.1 Flowchart of the IMPACT Mortality Model parameters



The fall in coronary heart disease deaths

The number of CHD deaths expected in 2000 if the mortality rates in 1981 had persisted was calculated by indirect age standardisation, using 1981 as a base year. The CHD deaths actually observed in 2000 were then subtracted to give the fall in CHD deaths between 1981 and 2000 *(Appendix 7).*

Patient categories included in the IMPACT England and Wales model

ICD9 Codes 410-414 (prior to 2000) and ICD10 codes I20-I25 (since 2000) correspond to Coronary Heart Disease. This definition consists of mainly myocardial infarction or angina. The specific patient groups comprised acute myocardial infarction, post myocardial infarction, unstable angina, chronic angina, CABG surgery, angioplasty, and heart failure.

Treatment categories included in the IMPACT England and Wales model

The model aimed to include all medical and surgical treatments given in 1981 and 2000 in England and Wales. These interventions are listed in *Box 8.9* and included all the interventions considered in earlier versions of the IMPACT Model[4;5] plus primary angioplasty for myocardial infarction, statins for primary prevention, platelet IIB/IIIA inhibitors for unstable angina, and spironolactone and beta-blockers for heart failure.

Mortality Reduction Estimation by treatments

The mortality reduction for each treatment was calculated using the relative mortality reduction reported in published meta-analyses and trials listed in *Box 8.2* applied to the case fatality observed in unselected patient cohorts[143;144]. Case fatality rates for patient groups are presented in *Appendix 8.* Survival benefit over a one-year time interval was used for all treatments, thus only DPPs for at least one year were counted in the calculations.

The deaths prevented or postponed for at least a year were therefore calculated as:

Patient numbers eligible X treatment uptake X relative mortality reduction X one-year case fatality

An example of calculation method is presented below in *Box 8.2*:

Box 0.2 Example of DPP calculation: Men aged 55-64 given aspirin for acute myocardial infarction

In the Antithrombotic Trialists' Collaboration meta analysis, aspirin reduced relative mortality in men with AMI by 15%[160]. In England and Wales in 2000, 10,699 men aged 55-64 were eligible, and 95% were given aspirin[289]. One year case fatality in men aged 55-64 admitted with an AMI was approximately 17%[143].

The DPPs for at least a year were therefore calculated as:

Patient numbers x treatment uptake x relative mortality reduction x one-year case fatality = 10,699 x 95% x 15% X 17% = 259 DPPs.

Polypharmacy Issues

Individual CHD patients may receive a number of different medications. However, RCT data on efficacy of treatment combinations are sparse. Mant and Hicks[323] suggested a **cumulative relative benefit** method to estimate the case-fatality reduction achieved by polypharmacy. The potential effect of multiple treatments in an individual patient were therefore examined using the Mant and Hicks approach:

Relative Benefit = 1 - [(1 -Treatment A) X (1-Treatment B) X…. (1-Treatment n)[323]**.**

An example of this approach and its use for IMPACT Model is presented in *Box 8.3* below:

Box 0.3 Example of Mant and Hicks calculation for secondary prevention following acute myocardial infarction.

If we take the example **of secondary prevention following AMI;** good meta-analysis evidence suggests that, for each intervention, the relative reduction in case fatality is approximately:

Aspirin 15%[160], beta-blockers 23%[166], ACE inhibitors 23%[167], statins 29%[34] and rehabilitation 27%[324].

The Mant and Hicks[323] approach, recently used by Wald and Law[325], suggests that in individual patients receiving all these interventions, case-fatality reduction is very unlikely to be simply additive ie not **117%** (15% + 23%+ 23% + 29% + 27%). Indeed, 117% is clearly absurd, implying immortality. Instead, having considered the 15% case fatality reduction achieved by aspirin, the next medication, in this case a beta-blocker, can only reduce the **residual** case fatality (1-15%). Likewise, the subsequent addition of an ACE inhibitor can then only decrease the **remaining** case fatality, which will be 1 - [(1- 0.15) X (1-0.23)].

The Mant and Hicks approach therefore suggests that a **cumulative relative benefit** can be estimated as follows:

Relative Benefit = 1 - [(1 -Treatment A) X (1-Treatment B) X (1 -Treatment C) X (1 - Treatment D) X (1 -Treatment E)]

In considering appropriate treatments for AMI survivors, applying relative reductions for aspirin, beta-blockers ACE inhibitors statins and rehabilitation then gives:

Relative Benefit = 1 - [(1 -aspirin) X (1 - beta-blockers) X (1 - ACE inhibitors) X (1- statins) X (1- rehabilitation)]

= 1 - [(1- 0.15) X (1-0.23) X (1-0.23) X (1- 0.29) X (1- 0.27)]

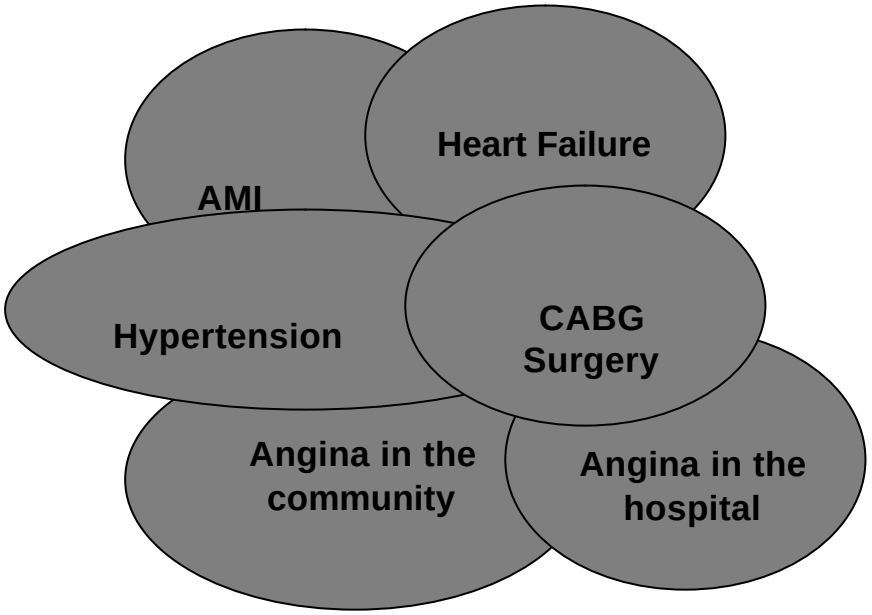
= 1 - [(0.85) X (0.77) X (0.77) X (0.71) X (0.73)]

= **0.74 ie a 74% lower case fatality**

Potential overlaps between patient groups: avoiding double counting

There are potential overlaps between CHD patient groups *(Figure 8.1).* For example, approximately half the patients having CABG surgery have a previous AMI[326], 20-30% of AMI survivors develop heart failure within 12 months[174], and over 50% of CHD patients have a history of hypertension[143] *(Figure 8.1).*

Figure 0.2 Potential overlaps between CHD patient groups



Therefore, to avoid double counting, potential overlaps between different groups of patients were identified and appropriate adjustments were made by subtracting one group from another. For instance, I subtracted the number of severe heart failure patients treated in hospital from the total number of heart failure patients in the community (because community heart failure patients could be admitted to hospital on one or more occasions).

A comprehensive list of overlap assumptions is presented in *Box 8.4.*

Box 0.4 Assumptions and overlap adjustments used in IMPACT Model.

Treatment category	Assumptions and Overlap Adjustments	Justification
PTCA patients progressing to CABG surgery	– PTCA numbers multiplied by 0.8, assuming that 20% of PTCA go to CABG	Martin (2002)[327]
Efficacy of PTCA in Angina	- Assumed equivalent to CABG surgery for two vessel disease (maximum estimate), or equal to medical therapy (minimum estimate)	Sculpher (1994)[328] Folland (1997)[329] Yusuf (1994)[330]
Angina in the community	From the total patient numbers with angina in the community, first deducted: – Patients already treated for unstable angina in hospital, – 50% of those receiving CABG for angina, – 50% of those receiving secondary prevention post AMI/post CABG/Post Angioplasty,	Capewell (2000)[143]
Heart failure in the community	– Assume 50% of heart failure is due to CHD – Deduct patients treated for severe heart failure in the hospital	Fox (2001)[174]
Hypertension treatment: overlaps with other CHD patient groups	– Total hypertensive patient numbers in community calculated, then deduct: – 50% of post AMI patients – 50% of community angina patients – 50% of community heart failure patients	Health Survey for England 1998[48]
Fall in population blood pressure	– Estimate the number of DPPs by hypertension treatment – Then subtract this from the total DPPs attributed to the fall in population blood pressure	Capewell *(*1999)[4] Capewell (2000)[5]
Post MI patients	– Assume 50% overlap between post-MI and post-CABG patients	Capewell (2000)[5]

Patient compliance and adherence

Low compliance to prescribed medical interventions is a complex problem especially for patients with chronic diseases. In this model, compliance, the proportion of treated patients actually taking therapeutically effective levels of medication, was assumed to be 100% in hospital patients (because of their continuous supervision by health care staff), 50% in asymptomatic community patients (on the basis of available evidence[331]) and 75% in symptomatic community patients (as a value intermediate between 50% and 100%). Each assumption was subsequently tested in a sensitivity analysis, as described later in this chapter.

Deaths prevented or postponed by therapies in 1981

A number of effective therapies were already in limited use in 1981. These included CABG surgery, cardiopulmonary resuscitation, beta-blockers for acute myocardial infarction, diuretics for acute left ventricular heart failure, and therapy for moderate and severe hypertension (defined as a diastolic blood pressure >105mmHg). Precise patient data for some of these interventions, including CABG, and eligible hypertensives, were available from the data sources detailed below. Others, such as beta-blocker use for post MI patients and heart failure treatment in hospital and in the community were estimated after consultation with cardiologists in practice in 1981. Again, each assumption was subsequently tested in a sensitivity analysis.

Risk factors included in the model

The review of CHD epidemiology in *Chapter 2*, identified and discussed the key risk factors for CHD. The original Scottish IMPACT only considered the major risk factors, smoking, cholesterol and blood pressure. These were retained in the IMPACT Model for England and Wales, and attempts were made to incorporate additional risk factors such as diabetes, obesity, physical activity and deprivation.

As I discussed in *Chapter 2*, diabetes is an independent risk factor for CHD[21;42] and it is estimated that up to 80% of adult diabetic patients die of CVD, and 75% of these deaths are caused by CHD[45]. For modelling purpose, diabetes trend data was available from various studies and surveys in England and Wales, although with some limitations.

Obesity is also found to be a significant independent risk factor for CHD incidence[50;51] and data on obesity trend was available from national surveys.

Physical inactivity is associated with at least a twofold increase in CHD risk[52]. Although adjusting for other cardiovascular risk factors weakens this association, the beneficial effect of physical activity remains statistically significant[53].

CHD showed a strong social class gradient. The death rate from CHD is approximately 3 times higher among unskilled manual men of working age than among professional men[81]. Data on deprivation and household income were available from routine statistics in the UK[305;332].

While inclusion of a number of other risk factors were considered desirable, pilot work demonstrated the lack of reliable population-based data in 1981, or 2000 or both eg low birth weight for foetal origins of disease. However, the model still included all the main risk factors which together have been generally considered shown to explain at least 75% of CHD risk[333].

Calculating the mortality benefits from changes in specific risk factors

For risk factor changes, the model employs regression (β) coefficients obtained from large cohort studies and MONICA analyses. Each β coefficient quantifies the independent relationship between population change in a specific CHD risk factor, (such as smoking, cholesterol, or blood pressure) and the consequent change in population CHD mortality rate, having adjusted for all other factors considered in that particular analysis. These coefficients were reviewed and summarised in Box 8.12.

It has been shown in several studies that the association between blood pressure and CHD is continuous and that a threshold was difficult to detect [24;27]. Similar findings apply to serum total cholesterol levels and CHD risk. A β coefficient is therefore very appropriate to quantify the population mortality impact of change in each specific risk factor.

The population attributable risk fraction method offers an alternative approach when a) there is a threshold or b) there are insufficient data to generate a reliable β coefficient (for instance diabetes, obesity, activity and deprivation).

The β coefficient approach is preferable for several reasons. Firstly, it is usually more stable across populations, particularly when based on a meta-analysis. Secondly, it usually involves a more reliable adjustment for other factors in a multi-variate analysis. Thirdly, PARs may overestimate achievable impact from a risk factor change (they are often based on RRs obtained from a dichotomised risk factor and population prevalence). Fourthly, the RR of a risk factor is very sensitive to how many other risk factors were included or excluded in the original statistical model[334]. For instance, the PAR quoted for physical inactivity can range from less than 10%[335] up to 37%[336].

The DPPs between 1981 and 2000 by the fall in each risk factor was then calculated as the product of three variables:

CHD deaths in that group in 1981 base year X relative risk factor decline X b coefficient

An example of this calculation is given below:

Box 0.5 Example of mortality fall estimation attributable to change in population risk factor (smoking).

Mortality fall due to reduction in smoking prevalence in women aged 55-64:

In England and Wales smoking prevalence in women aged 55-64 fell from 39% to 23% between 1981-2000, an absolute reduction of 16%, and a relative reduction of **41%, (16/39)**.

Pooling of studies from Finland, Iceland and elsewhere[187;192;337] produced a β coefficient value of **0.51.** (That is to say for every percent fall in smoking prevalence, the population CHD mortality would be expected to fall by 0.51%.)

The DPPs between 1981 and 2000 were then calculated as:

CHD deaths in that group in 1981 base year X risk factor decline X b coefficient:

Thus

5,555 X 41% X 0.51 = 1,162 DPPs.

This calculation was then repeated

a) for men and women in each age group, and

b) for each risk factor

c) using maximum and minimum values in each group, to generate a sensitivity analysis

Population Attributable Risk Fraction Method

A separate method was used for obesity, diabetes, physical activity and socio-economic deprivation, because of the absence of suitable β coefficients[4;5]. Population attributable risk fraction (PAR) was calculated using the conventional formula *(Box 8.6).*

These risk factors were dichotomised and prevalences were obtained from population studies and surveys[48]. Obesity was defined as BMI>30 kg/m^2, diabetes was defined as clinically diagnosed diabetes[303], physical inactivity as moderate activity less than 3 times a week[48].

The number of CHD deaths attributable to each specific risk factor was calculated for 1981 and for 2000. The difference between the two values then represented the DPPs due to the change in that specific risk factor in the population.

An example of this calculation method is presented below in *Box 8.6.*

Box 0.6 Example of CHD mortality change estimation due to change in diabetes prevalence

Mortality change due to change in diabetes prevalence in men aged 75-84

The number of CHD deaths attributable to diabetes in 1981 and in 2000 was calculated using the PAR fraction. This required estimates of **P**, diabetes prevalence in both years[48;303;304], and **RR**, the relative risk of diabetes for CHD mortality (obtained from the EPIC Study[338]), and the number of deaths from CHD in each year. The population attributable risk fraction was then calculated as;

$$PAR = \frac{\text{Prevalence} \times (\text{Relative Risk} - 1)}{(\text{Prevalence} \times (\text{Relative Risk} - 1)) + 1}$$

In England and Wales, the diabetes prevalence in men aged 75-84 was 4% in 1981 and 7% in 2000. Thus 12% of CHD deaths were attributable to diabetes in 1981 and 18% in 2000 respectively *(Table below).* The number of actual deaths attributed to diabetes was then calculated: 2865 in 1981 and 3,916 in 2000. The difference between these (1,051) represented the change in the number of deaths attributable to the change in diabetes prevalence in the population between 1981 and 2000 (Table).

Table. CHD deaths due to diabetes in 1981 and 2000 in men aged 75-84

	Diabetes Prevalence			CHD deaths		PAR Fraction		Deaths attributable to Diabetes		Mortality Increase
Aged	1981	2000	RR	1981	2000	1981	2000	1981	2000	
65 - 74	a	b	c	d	e	f [i]	g[ii]	f*d	g*e	(f*d) – (g*e)
Best	**0.04**	**0.07**	**4.00**	**24205**	**21772**	**0.12**	**0.18**	**2865**	**3916**	**-1051**

i $f=(a \times (c-1)/((a \times (c-1))+1))$, ii $g=(b \times (c-1)/((b \times (c-1))+1))$

This calculation was then repeated

a) for men and women in each age group, b) for obesity, physical inactivity and deprivation and c) using maximum and minimum values in each group, to generate a sensitivity analysis

Estimating deaths prevented or postponed by changes in deprivation using the PAR approach

Since satisfactory independent beta coefficients did not exist for deprivation, a population attributable risk (PAR) approach was used.

Deriving the age-specific PARs for deprivation

No recent England and Wales data were available on the socio-economic gradients in CHD mortality. I therefore used the best available alternative, social gradients in AMI mortality rate per 100,000 in the Scottish men categorised by quintiles of deprivation measured as Carstairs deprivation score (Unpublished data from SLiDE Study)[339] (Table 8.1).

Table 0.1 Social gradients in AMI mortality rates (per 100,000) in the Scottish population 1986-1995 (quintiles of deprivation in men)

	AGE GROUPS		
Deprivation Quintile	**25-64 years**	**65-74 years**	**>75 years**
Most affluent (1)	1.63	16.08	27.92
2	1.99	17.99	30.18
3	2.13	18.49	29.63
4	2.50	19.17	16.54
Most deprived (5)	2.81	20.07	29.52
Rate Ratio	**1.72**	**1.25**	**1.06**
PAR 5 v 1*	**0.126**	**0.047**	**0.011**

*Prevalence of people in the fifth quintile of deprivation category is 20%.

Rate ratios estimated for most deprived quintile were 1.72, 1.25 and 1.06 in men aged 25-64, 65-74 and >75 respectively. These RRs were consistent with the RRs reported in other studies[340]. The crude PAR values for AMI mortality in the most deprived quintile compared with the most affluent were then calculated as: 0.126 for ages 25-64 years, 0.047 for 65-74 and 0.011 for men aged >75 years *(Table 8.1).*

Changes in deprivation in England and Wales 1981-2000

After considering and testing various options, the most dependable measure of change in deprivation was considered to be the data available on Final Household Income, adjusted for tax and benefits, and adjusted for inflation between 1981 and 2000[332]. Between 1981 and 2000, income in the most deprived quintile increased from £3,220 to £4,410, after adjusting for tax, benefits, and inflation *(Table 8.2).*

Table 0.2 Changes in household income 1981-2000, adjusted for tax, benefits and inflation

	Household income (£)					
	1981	1999 Crude	Inflation adjustment	1999 adjusted	Absolute change indexed to 1981	% change
Quintiles	**a**	**b**	**c**	**d=b/c**	**e=d-a**	**f=e/a**
Most affluent	12,260	35,440	2.0	17,720	5,460	0.45
2	7,670	20,380	2.0	10,190	2,520	0.33
3	5,790	15,840	2.0	7,920	2,130	0.37
4	4,130	11,470	2.0	5,735	1,605	0.39
Most deprived	**3,220**	**8,820**	**2.0**	**4,410**	**1,190**	**0.37**

It was then (generously) assumed that reduction in deprivation was equal to increase in household income.

Estimating the number of CHD deaths prevented or postponed by improvement in deprivation

31,632 CHD deaths occurred in men aged 65-74 in 1981 *(Appendix 7).* If the PAR is 0.038, then approximately 1,195 of these deaths could be attributable to being in the lowest deprivation quintile (0.038 x 31,632), *(Table 8.3).*

Thus, approximately 442 deaths were prevented or postponed by a 37% improvement in income/deprivation 1981-2000 *(Table 8.3).*

Table 0.3 Deaths prevented or postponed by improvements in deprivation, using PAR methodology

	CHD deaths 1981	Attributable fraction (PAR)	CHD deaths attributable to deprivation in 1981	Relative reduction in deprivation	Mortality Reduction 1981/2000
	a	b	(a x b)	c	(a x b x c)
Men, aged 65-74	31,632	0.038	1,195	0.37	**442**

Model Validation: Comparison with observed mortality falls

The model **estimate** for the total DPPs by all treatments plus all risk factor changes (or increase in the case of obesity, diabetes and physical inactivity) was summed and then compared with the **observed** falls in mortality for men and women in each specific age group. On an *a priori* basis, any shortfall in the overall model estimate was then formally attributed to other, unmeasured risk factors[3-5].

Sensitivity Analyses

Because of the uncertainties surrounding many of the values, a multi-way sensitivity analysis was performed using Brigg's analysis of extremes method[231;341]. Minimum and maximum mortality reductions were generated for therapeutic effectiveness, using 95% confidence intervals for relative risk obtained from the most recent meta-analyses or large randomised controlled trials and the minimum and maximum plausible values for the remaining key parameters: Patient numbers, treatment uptake and adherence were based on the quality of the available data: eligible patient numbers $\pm$ 10%[196;201], treatment uptake $\pm$ 50%, and compliance $\pm$30%[331]. Corresponding sensitivity analyses were constructed for risk factors, the key parameters being the β coefficient, relative risk, change in risk factor and CHD death numbers in base year.

Illustrative examples of sensitivity analyses and calculations are shown in the *Box 8.7:*

Box 0.7 Example of sensitivity analysis for benefits from treatments given to CHD patients.

Sensitivity analysis for mortality reduction estimation for men aged 55-64 given aspirin for acute myocardial infarction:

In the ATT meta analysis, aspirin reduced relative mortality in men with acute myocardial infarction by 15%[160]. In England and Wales in 2000, 10,699 men aged 55-64 were eligible, and 95% were given aspirin[289]. One year case fatality in men aged 55-64 admitted with an acute myocardial infarction was approximately 17%[143].

The DPPs for at least a year were therefore calculated as:

Patient numbers x treatment uptake x relative mortality reduction x one-year case fatality = 10,699 x 95% x 15% X 17% = 259 DPPs.

	Patient numbers	**Treatment Uptake**	**Relative Mortality reduction**	**One year case fatality**	**DPPs**
	a	**b**	**c**	**d**	**(a x b x cxd)**
Best Estimate	**10,699**	**0.95**	**15%**	**17%**	**259**
Minimum estimate	9,629	0.48	11%	14%	**71**
Maximum estimate	11,769	0.99	19%	22%	**487**

This may be described as a "robust" approach for two reasons.

a) maximum and minimum values for each variable were deliberately forced to provide a wider range rather than a narrower one, eg relative mortality reduction $\pm$20% rather than say, $\pm$10%.

b) the resulting product, for instance the minimum estimate, was generated by assuming that the lowest feasible values all occurred at the same time, a most unlikely situation.

1.15 Identification and assessment of relevant data for IMPACT Model

In *Chapter 7*, I presented and evaluated the CHD data sources in the UK. The review showed that available information on CHD in the UK is frequently patchy, obsolete or not available. Although the data are scarce with a good assessment of data quality and assumptions or extrapolations they might still be used for modelling. In this section I would like to present how I identified and assessed the data used for IMPACT Model.

To build the IMPACT Model a wide range of data was needed from many different sources. Information on population, demographic changes, mortality and myocardial infarction incidence was principally obtained from routine health statistics from the Office for National Statistics (ONS) and the British Heart Foundation's Annual CHD Statistics[2]. The number of patients admitted to hospital with myocardial infarction, angina and heart failure was obtained from Hospital Episode Statistics (HES). Patients undergoing cardio-pulmonary resuscitation (CPR) in the community or in hospital were enumerated from various surveys. Information on patients undergoing CABG surgery and angioplasty came from the United Kingdom Cardiac Surgical Register and the British Cardiovascular Intervention Society's Audit returns respectively[197;198]. Surviving patients eligible for secondary prevention therapies after myocardial infarction, CABG surgery or angioplasty were calculated using routine statistics and revascularisation registers *(Box 8.8).*

The number of patients in the community with treated or untreated hypertension or angina was calculated using the 1998 Health Survey for England and the British Regional Heart Study. The number of treated and untreated heart failure patients in the community was obtained from General Practice returns and survey data *(Box 8.8).*

Box 0.8 Population and patient data sources for England and Wales, 1981-2000.

Information	Source
Population (1981-2000) **Deaths by age and sex (1981-2000)** **CHD mortality rates**	Office for National Statistics[195;266;277;278] and British Heart Foundation Annual CHD Statistics[2].
Acute myocardial infarction patients	Hospital Episode Statistics(HES)[196] British Heart Foundation Annual CHD Statistics[2].
CABG surgery patients	UK Society for Cardiothoracic Surgeons of Great Britain and Ireland's web site (http://www.scts.org/doc/2102)[197]. Figures for England and Wales obtained by deducting numbers for Scotland and Ireland from UK total.
Angioplasty patients **Patient numbers eligible for secondary prevention**	British Cardiovascular Intervention Society's web site http://www.bcis.org.uk/audit/Bcis00.ppt. AMI survivors from Hospital Episode Statistics (HES)[196] plus SLiDE[143]. CABG and angioplasty patients from websites above.
Angina patients admitted to hospital categorised as a) emergencies or b) elective	Hospital Episode Statistics 1999-2000 (http://www.doh.gov.uk/hes/index.html)[196].
Angina patients in the community	Prevalence of 'ever experienced angina' from Health Survey for England 1998[48], and British Regional Heart Study[279].
Heart failure patients admitted to hospital **Heart failure patients in the community**	Hospital Episode Statistics 1999-2000 (http://www.doh.gov.uk/hes/index.html)[196] Prevalence from Key Health Statistics from General Practice 1998 report[201] and Stewart et al[286].

Information on treatment prescription and uptake was obtained from various national and local clinical audits and surveys *(Box 8.9).*

Box 0.9 Medical and surgical treatments included in the model: data sources for treatment uptake levels

TREATMENTS	**Treatment Uptake in 2000 (average)**	**Source (year)**
ACUTE MYOCARDIAL INFARCTION		
Cardio-pulmonary resuscitation		
Community	46%	Julian (2002)[159], UKHAS-Norris, 1998[157]
Hospital	99%	Julian (2002)[159], UKHAS-Norris, 1998[157]
	88%	Sayer (2000)[342]
Thrombolysis	65% (aged <65)	BRESUS- Tunstall-Pedoe (1992)[280]
	57% (aged>65)	
	54%	UKHAS-Norris, 1998[157]
	55%	Julian (2002)[159]
	50%	French (1996)[343]
	85%	Birkhead (1999)[284]
	Age gradient	Barakat (1999)[344]
Aspirin	79%	UKHAS-Norris, 1998[157]
	70%	Brown(1997)[270]
	86%	French (1996)[343]
Primary angioplasty	<1%	David Cunningham, Myocardial Infarction National Audit Project (MINAP) (2002)- *personal communication*
Intravenous beta-blockers	<5%	Hardy (1999) [345], Owen (1998)[346], Woods (1989)[347]
	6.6%	Ferguson (1999)[348]
	32%- 56%	Brown(1997)[270]
ACE INHIBITORS	19%	UKHAS-Norris (1998)[157]
	19%	UKHAS-Norris (1998)[157]
	6%-17%	Brown(1997)[270]

SECONDARY PREVENTION IN CHD PATIENTS		
Aspirin	61%-70%	Ryan (2001)[289]
	81%	EUROASPIRE II (2001)[269]
Beta-blockers	44%	EUROASPIRE II (2001)[269]
	80%	Myocardial Infarction National Audit Project (MINAP) (2002)
ACE inhibitors	27%	EUROASPIRE II (2001)[269]
	25%	Ryan (2001)[289]
Statins	20%	Reid (2002)[349]
	36%	Whincup (2002)[350]
	69% 10%-60% Men 9%-35% Women	EUROASPIRE II (2001)[269] Ryan (2001)[289]
	33% 55%M, 40%F	British Regional Heart Study (2001)[351] DeWilde (2002)[352]
	50%	Benner (2002)[353]
	36%	Jackevicius (2002)[354]
Warfarin	4%	EUROASPIRE II (2001)[269]
Rehabilitation	14%- 23% post AMI 33%- 56% post CABG	Bethel (2001)[355]
	34%	EUROASPIRE II (2001)[269]
CHRONIC ANGINA		
CABG surgery	100%	Society of Cardiothoracic Surgeons of Great Britain and Ireland[197], Martin (2002)[327]
Angioplasty	100%	British Cardiac Intervention Society (2002)[198], Martin (2002)[327]

Aspirin in community	50%	Ryan (2001)[289]
Statins in community	10%	Ryan (2001)[289]
	23%	Whincup (2002)[350]
	21%	BRHS (2001)[351]
	35% and 25%	Reid (2002)[349]
UNSTABLE ANGINA		
Aspirin & Heparin	60%	PRAIS Study- Collinson (2000)[356]
Aspirin alone	30%	PRAIS Study- Collinson (2000)[356]
Platelet glycoprotein IIB/IIIA inhibitors	50%	PRAIS Study- Collinson (2000)[356]
HEART FAILURE IN THE HOSPITAL		
ACE inhibitors	58%	Cleland (2002)[357]
Beta-blockers	28%	Cleland (2002)[357]
Spironolactone	10%	Cleland (2002)[357]
Aspirin	50%	Cleland (2002)[357]
Statins	32%	Cleland (2002)[357]
HEART FAILURE IN THE COMMUNITY		
ACE inhibitors	68%	Ellis (2001)[358]
Beta-blockers	17%	Cleland (2002)[357]
Spironolactone	12%	Cleland (2002)[357]
Aspirin	38%	Ellis (2001)[358]
Statins	43%	Cleland (2002)[357]
HYPERTENSION TREATMENT		
	59%	Health Survey for England 1998(2001)[130]
STATINS FOR PRIMARY PREVENTION		
	3%	Packham (2000)[359]

Data on the efficacy of therapeutic interventions were obtained from published randomised controlled trials, meta-analyses and cohort studies *(Box 8.10)*.

Box 0.10 Clinical efficacy of interventions: relative risk reductions obtained from meta-analyses, and randomised controlled trials*

TREATMENTS	Relative Risk Reduction	Source paper: First author (year)
ACUTE MYOCARDIAL INFARCTION		
Cardio-pulmonary resuscitation (CPR)		
Community CPR	10%	Julian (2002)[159], BRESUS Study-Tunstall-Pedoe(1992)[280], Cobbe(1996)[360]
Hospital CPR	30% aged <65 15% aged >65	Julian (2002)[159], BRESUS Study- Tunstall-Pedoe(1992)[280]
Thrombolysis	20%-30%	FTT, Collins(1996)[361] , Estess(2002)[362]
Aspirin	15%	Antithrombotic Trialists' Collaboration (2002)[160]
Primary angioplasty	30%	Cucherat (2000)[164]
Beta-blockers	4%	Freemantle (1999)[166]
ACE inhibitors	7%	Latini (1995)[165]
SECONDARY PREVENTION IN CHD PATIENTS		
Aspirin	15%	Antithrombotic Trialists'Collaboration (2002)[160]
Beta-blockers	23%	Freemantle (1999)[166]
ACE inhibitors	23%	Flather (2000)[167]
Statins	29%	Pignone (2000)[34]
Warfarin	15%	Lau (1992)[363]
Rehabilitation	27%	Brown (2003)[324]
CHRONIC ANGINA		
CABG surgery	39%	Yusuf (1994)[330]
Angioplasty	8%	Yusuf (1994)[330], Pocock (1995)[152], Folland (1997)[329]
Aspirin	15%	Antithrombotic Trialists' Collaboration(2002)[160]
Statins	29%	Pignone (2000)[34]

UNSTABLE ANGINA		
Aspirin alone	15%	Antithrombotic Trialists' Collaboration (2002)[160]
Aspirin & Heparin	27%	Oler (1996)[364]
Platelet glycoprotein IIB/IIIA inhibitors	9%	Boersma(2002)[365]
HEART FAILURE IN HOSPITAL PATIENTS		
ACE inhibitors	26%	Flather (2000)[167]
Beta-blockers	37%	Shibata (2001)[177]
Spironolactone	30%	Pitt (1999)[176]
Aspirin	15%	Antithrombotic Trialists' Collaboration (2002)[160]
Statins	29%	Pignone (2000)[34]
HEART FAILURE IN THE COMMUNITY		
ACE inhibitors	26%	Flather (2000)[167]
Beta-blockers	37%	Shibata (2001)[177]
Spironolactone	41%	Pitt (1999)[176]
Aspirin	15%	Antithrombotic Trialists' Collaboration (2002)[160]
Statins	29%	Pignone (2000)[34]
HYPERTENSION TREATMENT		
	11%	Collins (1990)[366]
STATINS FOR PRIMARY PREVENTION		
	29%	Pignone (2000)[34]

***Relative Risk calculated as 1- Odds Ratio**

Population risk factor trend data were obtained mainly from The British Regional Heart Study, the General Household Survey, and the Health Survey for England *(Box 6.11).*

Box 0.11 Data sources on cardiovascular risk factors in the UK, 1981-2000.

Cardiovascular Risk factors Information	Source	
	Initial Year (1981)	**Most Recent Year (2000)**
Smoking prevalence	General Household Survey 1980[273]	General Household Survey 2000[200]
Cholesterol	British Regional Heart Study[272]	Health Survey for England 1994 and 1998[48]. Glasgow MONICA and Belfast MONICA trends 1985-1995 also available for comparison[156]
Population blood pressure	The Dietary and Nutritional Survey of British Adults[295] and British Regional Heart Study[272]	Health Survey for England 1998[48]
Obesity	The Heights and Weights of Adults in Great Britain[297]	Health Survey for England 1998[48]
Physical activity	British Regional Heart Study[272]	Allied Dunbar Survey 1990[299], Department of Transport's Transport Statistics for Great Britain[298]
Diabetes	Poole Diabetes Study[303]	Health Survey for England 98[48], General Practice Research Database[304]
Deprivation	Trends in Household Income[332]	Trends in Household Income[332]

In general data sources provided necessary information for modelling with some limitations. These limitations were discussed in detail in *Chapter 7.*

Data on the mortality reduction from specific population cardiovascular risk factor changes: b **coefficients**

These were obtained from published randomised controlled trials, meta-analyses and cohort studies. A range of different coefficients describing the relationship between each separate risk factor and CHD mortality were presented below *(Box 8.12 and Box 8.13).* These coefficients represent % change in CHD mortality by 1 % change in mean population risk factors.

Box 0.12 Estimated b **coefficients from multiple regression analyses quantifying the relationship between changes in population mean risk factors and changes in CHD mortality for men aged under 65.**

	b **Coefficients**		
Study	**Smoking**	**Cholesterol**	**Blood Pressure (diastolic)**
Sigfusson 1991[337]	**0.51**	2.22	1.06
Law *et al.* 1994[32]	-	**1.9 – 5.4***	
Vartiainen *et al.* 1994[192]	0.70	2.00	**1.67**
MONICA, 2000[125]	0.73	1.31	0.53
Collins/MacMahon, 1990[24;366]	-	-	2.08
Seven Countries[367;368]	-	2.10	2.09
Our 'best' estimates	**0.51**	**2.46**	**1.67**
Minimum	0.40	1.31	0.53
Maximum	0.73	3.00	2.09

*adjusted for regression dilution bias

The MONICA study considered the impact of changes in risk factors on changes in CHD mortality at a ***population*** level. However, the MONICA coefficients have been criticised for 'ecological bias' and may underestimate the relationship between changes in risk factors and population trends in CHD mortality. This is because:

1) those who do not respond to risk factor surveys may be at higher risk than attendees, and a decreasing response rate to MONICA surveys was observed over the course of the study[125].

2) the major outcome from the MONICA study was all coronary events, not just CHD mortality, which may slightly dilute the β coefficients obtained.
3) MONICA coefficients do not account for possible regression dilution bias; adjusted coefficients may be as much as 60% higher[32].
4) The principal MONICA estimates made no allowance for a possible lag time between changes in the risk factor levels and changes in population CHD mortality[125].

The MONICA coefficients for cholesterol and diastolic blood pressure are generally lower than from other sources[192;368] and have thus been used in our model as minimum estimates using the data for males only. In many MONICA centres, the number of events among females was too small to obtain reliable estimates, and the smoking coefficient appeared particularly anomalous.

The coefficients derived from meta-analyses and the largest cohort studies were therefore regarded in our model as the best estimates. The best estimates were taken from the Sigfusson study in Iceland for smoking[337], from the Law meta-analysis for cholesterol[32] and Finland for blood pressure[192]. Maximum estimates for cholesterol were taken from Law *et al*[32], for smoking from MONICA[125] and for blood pressure from the Seven Countries[367;368].

Minimum estimates for cholesterol and blood pressure came from MONICA Study[125]. The coefficients were reduced in older age groups to reflect good epidemiological evidence suggesting that relative risk is attenuated by age[32].

In the sensitivity analyses, the England and Wales IMPACT model proved to be stable with a range of beta coefficients.

There were no suitable Beta coefficients describing the individual relationships between obesity, diabetes, physical inactivity, and deprivation with CHD mortality. Relative Risks were therefore taken from the largest and most recent studies available *(Box 6.13).*

Box 0.13 Relative risks for obesity, diabetes, physical inactivity and deprivation and coronary heart disease mortality *(Best, minimum and maximum estimates).*

	Relative Risk (95% Confidence Interval)			
	Obesity (BMI>29kg/m^2)	**Diabetes** (clinically diagnosed)[303]	**Physical activity** (moderate activity 3 times a week)[48]	**Deprivation** (Carstairs score, most deprived 5th quintile, based on SliDE data)[339]
Men	Stevens (1998)[369], RRs ranged from 1.57 to 2.33# by age groups.	Khaw (2001)[338], RR=4.24*(1.92-9.35)	Shaper (1991)[53] RR=0.50** (0.2-0.8)	Smith (1998), Renfrew and Paisley Study340. RR=1.24(1.03-1.49)+
Women	Stevens (1998)[369], RRs ranged from 1.00 to 2.24# by age groups. Willett (1995)[50] RR=3.56 (2.96-4.29)	Female RRs x 1.5 higher than male, (Members of the British Diabetic Association Study)[370].	Lee (2001)[371], RR=0.55*** (0.37-0.82)	Smith (1998), Renfrew and Paisley Study340. RR=1.44 (1.15-1.80)+

Adjusted for age, education, physical activity, alcohol consumption.

* Adjusted for age, serum cholesterol, systolic blood pressure, smoking, BMI, MI or stroke history.

** Adjusted for BMI, social class, smoking, total cholesterol, HDL cholesterol, FEV1, breathlessness and heart rate.

***Adjusted for age, treatment, smoking, alcohol, fat consumption, fibre, fruits and vegetables, use of hormones, postmenopausal status, parental history of MI at an early age.

+ Adjusted for age, blood pressure, cholesterol, BMI, FEV1 score, smoking, angina, ECG ischeamia, bronchitis and social class.

In this chapter, I have described the IMPACT Model and methodology. In the next chapter, I will describe how I then attempted to use the IMPACT Model to analyse the recent CHD mortality trends in England and Wales.

EXPLAINING THE DECLINE IN CHD MORTALITY IN ENGLAND AND WALES BETWEEN 1981 AND 2000

Having described the IMPACT Model and methodology in the previous chapter, I will now describe how I then examined the CHD mortality trends in England and Wales between 1981 and 2000.

1.16 Introduction

Since the 1970s, CHD mortality rates have halved in most industrialised countries but somewhat less in the UK[2]. Explanations for the mortality falls remain controversial[156]. Many authors credit the increasingly widespread use of effective therapies such as thrombolysis, aspirin, ACE-inhibitors, statins and coronary artery bypass surgery[372;373]. Others highlight reductions in major cardiovascular risk factors such as smoking, cholesterol and blood pressure[119;156]. While both components are probably important, answering this complex question appears difficult.

Some researchers have therefore used models of varying degrees of sophistication to try and explain the observed declines in CHD mortality[3]. The majority consistently suggest that risk factor improvements explain more of the mortality decline than do treatments. For example, it has been estimated that the proportion of mortality decline attributable to risk factor reductions was 57% in the USA between 1980 and 1990[233], 60% in Auckland, New Zealand between 1974 and 1981[194] and 52% between 1982 and 1993[5], and 60% in Scotland between 1975 and 1994[4]. Since then, however, many effective therapies have been introduced[148].

A better understanding of the CHD mortality fall in Britain and other countries is clearly essential, both to predict future trends and to clarify policy options for CHD prevention[148;374]. I have therefore examined how much of the fall in CHD mortality in England and Wales between 1981 and 2000 can be attributed to 'evidence based' medical and surgical treatments, and how much to changes in major cardiovascular risk factors.

1.17 Methods

In the cell-based IMPACT mortality model, described in *Chapter 8,* I identified and incorporated data for men and women aged 25 to 84 years in England and Wales detailing; a) CHD patient numbers, b) uptake of specific medical and surgical treatments, c) population trends in major cardiovascular risk factors (smoking, total cholesterol, hypertension, obesity, diabetes, physical activity and socio-economic deprivation), d) effectiveness of specific cardiological treatments, and e) effectiveness of specific risk factor reductions.

The methods used and identification and assessment of relevant data for English IMPACT Model were presented in *Chapters 7 and 8* therefore only results and discussion will be presented here.

1.18 Results

In England and Wales between 1981 and 2000, CHD mortality rates fell by 62% in men and 45% in women aged 25-84. There were 68,230 fewer CHD deaths than expected from baseline mortality rates in 1981 *(Appendix 7).*

Medical and surgical treatments *(Table 9.1)*

Medical and surgical treatments together prevented or postponed approximately 25,765 deaths (minimum estimate 15,390, maximum estimate 45,265). This represented approximately 42% of the total CHD mortality fall, after allowing for treatments given in 1981 *(Figure 9.1).* Substantial contributions came from treatments in individuals for secondary prevention (11.2%), heart failure (12.6%), acute myocardial infarction (7.7%), angina (7.0%), and hypertension (3.1%).

Approximately 4,740 deaths were prevented or postponed by immediate treatments for acute myocardial infarction; the biggest contributions came from cardiopulmonary resuscitation, aspirin and thrombolysis. CABG surgery and PTCA were estimated to prevent or postpone approximately 1,935 and 559 deaths respectively, accounting for 3.8% of the total *(Table 9.1).*

Adjustment for polypharmacy in individual patients

Applying the Mant and Hicks equation to the uptake of multiple medications in individual patients would reduce the total DPPs (25,765) by approximately 2,118 (395 in acute myocardial infarction, 800 in heart failure patients and 923 in secondary prevention) *(Appendix 9).*

Figure 0.1 Coronary heart disease deaths prevented or postponed by treatments and risk factor changes in the England and Wales population between 1981 and 2000.

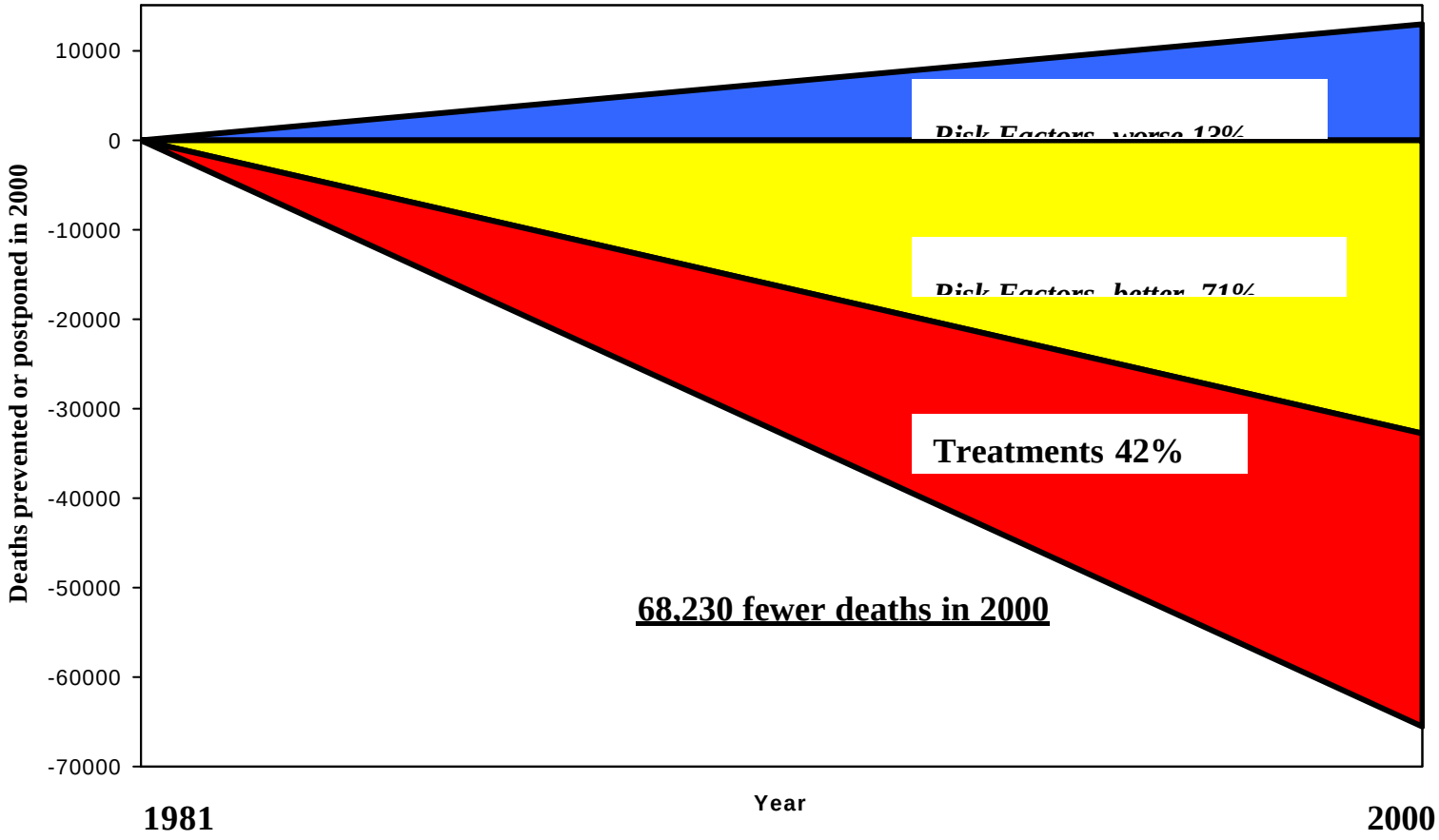


Table 0.1 Deaths prevented or postponed (DPP) by medical and surgical treatments in England and Wales in 2000.

TREATMENTS	Patients eligible	Treatment uptake	Deaths prevented or postponed			Proportion of overall DPPs (%)		
		(%)*	Best Estimate	*Minimum estimate*	*Maximum estimate*	Best Estimate	*Minimum estimate*	*Maximum estimate*
Acute myocardial infarction	**66,195**		**4,740**	**3,225**	**8,290**	**7.7**	**5.2**	**13.5**
Community Resuscitation	(3,045)	48%	800	740	960	1.3	1.2	1.6
Hospital Resuscitation	(7,280)	99%	1,455	680	2,185	2.4	1.1	3.5
Thrombolysis		46%	1,320	600	1,995	2.1	1.0	3.2
Aspirin		94%	1,950	1,130	2,780	3.2	1.8	4.5
Primary angioplasty		1%	40	15	205	0.1	0.0	0.3
Beta-blockers		4%	20	10	40	0.0	0.0	0.1
ACE inhibitors		19%	170	45	125	0.3	0.1	0.2
Secondary prevention			**6,900**	**4,585**	**12,670**	**11.2**	**7.4**	**20.6**
2' prevention post infarction	**313,380**		**3,844**	**2,850**	**5,060**	**6.2**	**4.6**	**8.2**
Aspirin		56%	1,240	640	1,990	2.0	1.0	3.2
Beta-blockers		34%	970	570	1,635	1.6	0.9	2.7
ACE inhibitors		19%	440	335	1,440	0.7	0.5	2.3
Statins		25%	460	430	1,340	0.7	0.7	2.2
Warfarin		4%	100	60	235	0.2	0.1	0.4
Rehabilitation		23%	675	305	1,230	1.1	0.5	2.0
2' prevention post revascularisation	**315,680**		**3,055**	**1,735**	**7,610**	**5.0**	**2.8**	**12.4**
Chronic Angina			**3,425**	**1,905**	**5,890**	**5.6**	**3.1**	**9.6**
CABG surgery (1990-2000)	187,415	100%	1,935	1,125	2,375	3.0	1.8	3.8
Angioplasty (1990-2000)	112,405	100%	560	160	815	0.8	0.3	1.3
Aspirin in Community	1,763,635	55%	1,105	625	2,115	1.6	1.0	3.4
Unstable Angina	**67,375**		**910**	**620**	**1,620**	**1.5**	**1.0**	**2.6**
Aspirin & Heparin		59%	465	335	720	0.8	0.5	1.2
Aspirin alone		30%	235	125	655	0.4	0.2	1.1
Platelet IIB/IIIA Inhibitors		48%	210	160	245	0.3	0.3	0.4

TREATMENTS Table 9.1 (Continued)	Patients eligible	Treatment uptake (%)*	Deaths prevented or postponed			Proportion of overall DPPs (%)		
			Best Estimate	*Minimum estimate*	*Maximum estimate*	Best Estimate	*Minimum estimate*	*Maximum estimate*
Heart failure- total			**7,760**	**4,162**	**13,596**	**12.6**	**6.8**	**22.1**
Heart failure- in hospital	**34,690**		**4,755**	**2,295**	**7,680**	**7.6**	**3.7**	**12.5**
ACE inhibitors		62%	1,850	635	2,625	3.0	1.0	4.3
Beta-blockers		31%	1,280	745	2,270	2.1	1.2	3.7
Spironolactone		10%	350	220	675	0.6	0.4	1.1
Aspirin		50%	870	405	1,535	1.4	0.7	2.5
Statins		21%	410	290	575	0.7	0.5	0.9
Community heart failure	**242,090**		**3,210**	**1,940**	**6,320**	**5.0**	**3.1**	**10.3**
ACE inhibitors **		56%	1,535	1,020	3,050	2.5	1.7	4.9
Beta-blockers**		15%	550	330	885	0.9	0.5	1.4
Spironolactone		10%	205	125	415	0.3	0.2	0.7
Aspirin		29%	585	350	1,480	1.0	0.6	2.4
Statins**		17%	335	110	490	0.5	0.2	0.8
Hypertension Treatment	**13,352,870**	53%	**1,890**	**840**	**2,785**	**3.1**	**0.0**	**4.5**
Statins for primary prevention	**7,630,760**	**3%**	**145**	**45**	**410**	**0.2**	**0.0**	**0.7**
Total Treatment Effects- 2000			**25,765**	**15,390**	**45,265**	**41.8**	**27.7**	**73.5**

* Treatment uptake levels are weighted averages of age specific uptake levels **Treatment efficacy for these groups was reduced by 25% assuming that only about 50% were on the optimal treatment dose.

Major cardiovascular risk factors *(Table 9.2)*

Changes in the major cardiovascular risk factors together produced a best estimate of 35,830 fewer deaths (minimum estimate 23,155, maximum 62,555) *(Table 9.2).* This therefore accounted for some 58% of the total mortality fall between 1981 and 2000. The biggest contribution came from the reduction in smoking (48.2%), along with decreases in serum total cholesterol levels (9.4%), blood pressure (9.5%) and deprivation (3.5%) *(Table 9.2).* These mortality reductions reflected a substantial decline in smoking prevalence and smaller reductions in mean blood pressure, total cholesterol and deprivation *(Table 9.2).*

Adverse trends were seen for obesity, physical activity, and diabetes. They, together caused approximately 7,650 additional CHD deaths *(Table 9.2).* The prevalence of obesity increased by 186%, resulting in an estimated additional 2,095 CHD deaths. Diabetes prevalence increased by 66% with approximately 2,890 additional CHD deaths, and indirect evidence suggested a 30% decrease in physical activity (with some 2,660 additional deaths *(Table 9.2).*

Table 0.2 Deaths prevented or postponed as a result of population risk factor changes in England and Wales 1981 and 2000.

RISK FACTORS	% Change in risk factor	Deaths prevented or postponed (number)			Proportion of overall DPPs (%)		
	1981-2000	Best Estimate	Minimum estimate	Maximum estimate	Best Estimate	Minimum estimate	Maximum estimate
Smoking	-34.5%	**29,715**	20,035	44,675	**48.2%**	32.5%	65.5%
Population blood pressure	-7.7%	**5,865**	4,245	15,470	**9.5%**	5.5%	20.6%
Cholesterol	-4.2%	**5,770**	3,930	12,100	**9.4%**	8.6%	27.0%
Deprivation	-6.6%	**2,125**	1,065	3,190	**3.5%**	1.7%	5.2%
Physical activity	- 30.6%	**-2,660**	-1,490	-3,460	**-4.3%**	-2.4%	-5.6%
Obesity	+186.2%	**-2,095**	-1,340	-2,585	**-3.4%**	-2.2%	-4.2%
Diabetes	+65.6%	**-2,890**	-2,565	-4,685	**-4.7%**	-4.2%	-7.6%
Total risk factor effects	-	**35,830**	23,155	62,555	**58.2%**	37.6%	76.2%

Table 0.3 Percent contribution of men and women to total DPPs by age groups in England and Wales (1981–2000).

	Total	25-34	35-44	45-54	55-64	65-74	75-84
Men	70%	89%	87%	85%	77%	64%	65%
Women	30%	11%	13%	15%	23%	36%	35%
Men /Women Ratio	**2.34**	**7.95**	**6.48**	**5.52**	**3.29**	**1.81**	**1.84**
Total DPPs	**61,595**	**185**	**1,510**	**6,625**	**13,750**	**21,065**	**18,460**

In year 2000 most of the DPPs due to cardiac treatments and risk factors changes in England and Wales came from men (70% in men and 30% in women). In younger age groups 85% to 90% of the DPPs were from men. After the age of 65, the ratio of DPPs in men compared with women decreased below 2 *(Table 9.3).*

Table 0.4 Percent contribution of treatments and risk factor changes to total DPPs in men and women by age groups in England and Wales (1981-2000).

	Men	25-34	35-44	45-54	55-64	65-74	75-84
Treatments	37%	19%	28%	33%	37%	42%	34%
Risk factors	63%	81%	72%	67%	63%	58%	66%
Total DPPs	**43,155**	**165**	**1,310**	**5,610**	**10,545**	**13,555**	**11,970**

	Women	25-34	35-44	45-54	55-64	65-74	75-84
Treatments	54%	69%	51%	50%	50%	48%	63%
Risk factors	46%	31%	49%	50%	50%	52%	37%
Total DPPs	**18,445**	**20**	**200**	**1,015**	**3,205**	**7,510**	**6,490**

In general, risk factor changes prevented or postponed more deaths in men compared with treatment effects (63% versus 37%). In women, the treatment effect was relatively greater, similar to risk factor changes in all age groups *(Table 9.4).*

Sensitivity Analyses, Validation and Model Fit

Figure 9.2 demonstrates the results of the sensitivity analysis. The proportional contributions of specific treatments and risk factor changes to the overall fall in CHD mortality in England and Wales between 1981 and 2000 remained relatively consistent *(Figure 9.2).* Thus, all secondary prevention treatments together accounted for approximately 11% of the total mortality fall of 68,230. The minimum contribution was 7% and the maximum 21%. This contribution therefore remained consistently larger than that for acute myocardial infarction or hypertension *(Figure 9.2).*

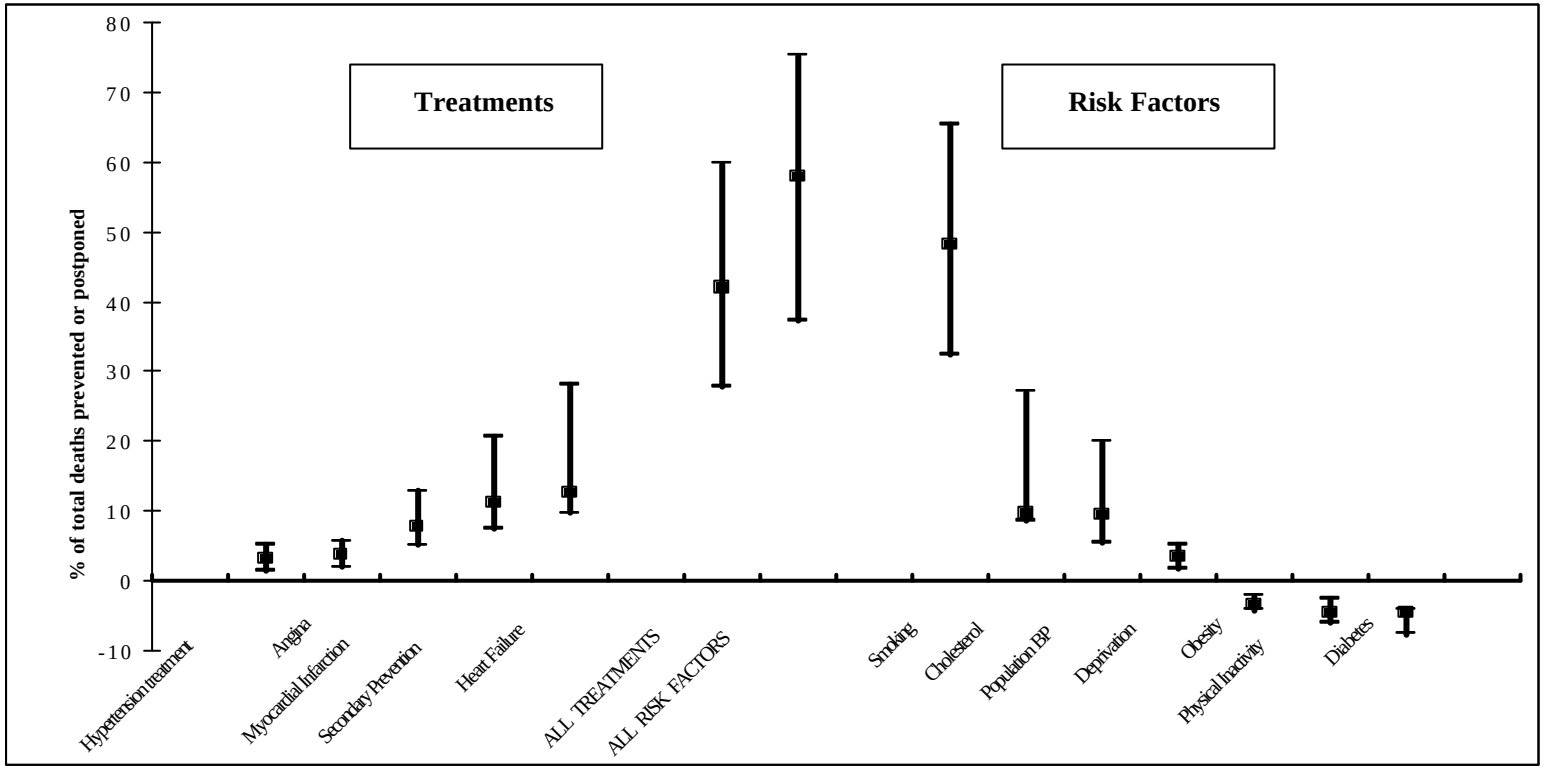
The agreement between the **estimated** and **observed** mortality falls for men and women in each age group was generally good *(Table 9.5).* Overall, the model accounted for 90% of the total mortality fall in England and Wales between 1981 and 2000, (96% in men and 79% in women). In general, the model estimates were close to the actual falls in men in all age groups. However, in women model fit less good , 79% overall and only 56% in women aged 75-84 years. As planned, the remaining 10% was attributed to other, unmeasured factors such as dietary changes and life-course effects.

Table 0.5 Model validation: estimated versus observed changes in CHD deaths in England and Wales 1981-2000.

	Age Group (years)						
MEN	**25-34**	**35-44**	**45-54**	**55-64**	**65-74**	**75-84**	**Total**
Estimated fall in CHD deaths	166	1,308	5,609	10,545	13,556	11,969	43,153
Observed fall in CHD deaths	168	1,314	5,571	10,685	15,342	11,740	44,822
Discrepancy	***-3***	***-6***	***37***	***-140***	***-1,786***	***229***	***-1,669***
Model Fit: Estimated fall / Observed fall in CHD deaths	**98%**	**100%**	**101%**	**99%**	**88%**	**102%**	**96%**
WOMEN	**25-34**	**35-44**	**45-54**	**55-64**	**65-74**	**75-84**	**Total**
Estimated fall in CHD deaths	21	202	1,015	3,204	7,510	6,492	18,444
Observed fall in CHD deaths	28	155	998	3,054	7,479	11,695	23,409
Discrepancy	***-7***	***47***	***17***	***150***	***31***	***-5,203***	***- 4965***
Model Fit: Estimated fall / Observed fall in CHD deaths	**76%**	**130%**	**102%**	**105%**	**100%**	**56%**	**79%**

Figure 0.2 Proportional contributions of specific treatments and risk factor changes to the CHD mortality reduction in England and Wales, 1981-2000: Results of a sensitivity analysis.

(¦ Best estimate, - minimum and maximum estimates)



1.19 Interpretation

CHD mortality in England and Wales fell by more than half between 1981 and 2000. Approximately 40% of this fall was attributable to the combined effects of modern cardiological treatments and almost 60% to reduction in major risk factors, particularly smoking. This is consistent with the majority of other studies in the USA[193], Europe[251], Scotland[4], and New Zealand[5]. Although Hunink et al attributed 71% of the recent US decline to 'treatments', this exception was more apparent than real, and principally reflected a different categorisation of risk factor falls in individual patients with recognized CHD. In the entire US population, 50% of the CHD mortality decline was actually explained by risk factor reductions[233]. Furthermore, Hunink et al did not report on specific medical therapies[233].

Modern cardiological treatments together prevented or postponed approximately 26,000 deaths in 2000. Irrespective of whether best, minimum or maximum estimates were used, the most substantial contributions came from secondary prevention and heart failure treatments. Revascularisation from CABG surgery and angioplasty together accounted for only 4% of the total mortality fall, much as in the USA[375]. This is a disappointingly small contribution, particularly when considering the large financial and political resources being consumed[148;205].

Thrombolysis likewise only accounted for one quarter of the deaths prevented by initial treatments for acute myocardial infarction. This was much less than aspirin and cardiopulmonary resuscitation, as in other studies[159]. Furthermore, treating angina patients with aspirin in the community prevented almost twice as many deaths as treating unstable angina patients in hospitals, principally reflecting the larger numbers involved *(Table 9.1).*

Treatment uptake levels were often poor *(Table 9.1).* This was more apparent for heart failure treatments in the community. Even though there were approximately ten times more eligible patients for heart failure treatments in the community, low treatment levels and sub optimal doses[269] resulted in fewer deaths prevented or postponed compared with hospital heart failure treatments *(Table 9.1).* Earlier work suggested that if even 80% of eligible patients had received appropriate therapy, approximately 30,000 additional deaths might have been prevented or postponed each year in the UK[4], equivalent to 100,000 fewer deaths in the USA.

Reductions in the major risk factors between 1981 and 2000 accounted for approximately 36,000 fewer deaths in England and Wales in 2000. The biggest single contribution reflected a large fall in smoking prevalence, from 39% to 28% overall. In sensitivity analyses, the maximum estimate for smoking decline impact remained consistently greater than all treatment effects combined *(Figure 9.2).* Almost 10% of the mortality fall came from a relatively small reduction (4.2%) in population total cholesterol level. This emphasises the large β coefficient of 1.9 –5.4[32], and highlights the potential gains from bigger reductions in population cholesterol. Other unquantified factors such as life-course effects, alcohol and other dietary improvements[55] accounted for approximately 10% of observed mortality reduction.

The adverse trends in obesity, diabetes and physical inactivity together contributed approximately 8,000 additional deaths in 2000. These cancelled out two decades of improvement in the fall of cholesterol levels. Furthermore, continuing deteriorations are expected[148;374;376.]

Modelling studies have potential strengths and limitations. These points will be discussed in detail in the discussion section of this thesis.

In conclusion, over half the recent CHD mortality fall in England and Wales was attributed to reductions in major risk factors, and some forty percent to medical therapies.

In this chapter I focused on CHD mortality trends in England and Wales. In the next chapter, I will consider what these DPPs might mean in terms of the years of additional life gained.

LIFE-YEARS GAINED FROM cardiological TREATMENTS and POPULATION RISK FACTOR CHANGES IN ENGLAND AND WALES, BETWEEN 1981 AND 2000

In the last chapter, I focused on CHD mortality trends in England and Wales between 1981 and 2000. I will now attempt to estimate the years of additional life gained in 2000.

1.20 Introduction

Life expectancy at birth in England and Wales increased by 4.4 years in men and 3.2 years in women between 1981 and 2000[377]. Much of this has been attributed to reductions in CHD mortality rates, which have halved in two decades. Much of the CHD mortality decline is attributed to the widespread use of effective therapies such as thrombolysis, aspirin, ACE-inhibitors, statins and CABG[372]. However, reductions in major risk factors such as smoking, cholesterol and blood pressure[119] have also made substantial contributions[373].

As I presented in earlier chapters, the majority of studies consistently suggest that improvements in treatment explain less than half of the mortality decline[3-5;194;233;248]. However, most such analyses have simply concentrated on mortality rather than a gain in longevity. Therefore in this chapter I estimated the life-years gained (LYG) due to cardiological treatments and to changes in cardiovascular risk factor levels that occurred between 1981 and 2000 in England and Wales.

1.21 Methods

Estimating the number of deaths prevented or postponed in England and Wales in 2000

The number of DPPs in 2000 that could be attributed to improved cardiac treatment uptake and risk factor changes since 1981 was estimated using the IMPACT CHD mortality model[248]. The number of CHD DPPs by each treatment group and risk factor changes was estimated as described in methods section in *Chapter 8.*

Median Survival Data

Medical and surgical treatments

For each treatment category, median survival was obtained from the best available population-based data[143;144]. Most came from a retrospective cohort study of unselected patients. This is the only UK dataset routinely linking all hospital admission records and all mortality data for an entire population of 5.1 million since 1981[143;144]. Age-specific median survival values came principally from a large, unselected cohort of 117,718 patients admitted to hospital with a first acute myocardial infarction (AMI)[143] and all 66,547 patients with a first admission for heart failure[144]. The first study also provides long-term survival data in all AMI survivors, including those developing heart failure[143]. Case fatality in subsequent admissions was approximately twice that in first admissions [143]. Median survival estimates for patients with hypertension were based on the mortality (between 7% and 29% dependent on age and sex) observed in the Glasgow Blood Pressure Clinic Cohort[378]. Estimates of survival following CABG surgery were obtained from local sources[379], and a recent cohort study in Scotland[380]. Angioplasty for angina was assumed to have no additional survival benefit[152]. *Appendix 10 and 11* detail the estimates of median survival for each category and their sources.

Deaths prevented or postponed by risk factor declines

Coronary atheroma generally begins early in life, symptomatic manifestations occur late and even then may go unrecognised. The deaths prevented by a risk factor reduction such as smoking cessation may therefore benefit an individual prior to or following the onset of symptomatic disease. Age-specific median survival in a patient with recognised CHD was assumed to be very similar to that in age-matched myocardial infarction survivors. Median survival in asymptomatic individuals was simply based on age specific life expectancy for the general population[377]. For the subjects with symptomatic but unrecognised CHD, median survival was assumed to lie midway between the values for myocardial infarction survivors[143] and the general population.

Calculation of life-years gained

The number of LYG in 2000 in each ten-year age group, for men and women in each treatment category and for each risk factor change, was then estimated as the product of the

number of DPPs in England and Wales in 2000, and the estimated median survival for that group.

An example of calculation method is presented below:

Men aged 65-74 given Beta-blockers for secondary prevention of myocardial infarction:

In a meta analysis it was estimated that Beta-blockers reduced mortality in men with post myocardial infarction by 23%[166]. In England and Wales in 2000, 18,180 men aged 65-74 were eligible, 33% were given Beta-blockers[269] and compliance to treatment was assumed to be 65%[354]. One year case fatality in men aged 65-74 with post myocardial infarction was approximately 7%[143]. The DPPs for at least a year were therefore calculated as:

Patient numbers x treatment uptake x compliance x relative mortality reduction x one-year case fatality = 18,180 x 33% x 65% x 23% x 7% = 63 DPPs.

Median survival was estimated to be 5.5 years in this group[143]. The number of LYGs was then estimated as: ***Deaths prevented or postponed x Median survival = 63 x 5.5 = 345 LYGs.***

Estimates of LYGs were adjusted to take into account the influence of 'competing causes of mortality[238;381]. This inflation was small, generally amounting to less than one extra year of life.

Sensitivity analyses

A sensitivity analysis was performed using the analysis of extremes method[231]. This addressed the uncertainties surrounding the key variables (patient numbers, treatment uptake and efficacy, the overlap between different treatment categories and median survival). Minimum and maximum estimates of LYGs were generated using 95% confidence intervals where available, otherwise the minimum and maximum plausible values for each variable[231] were used *(Appendix 10 and 11).*

1.22 Results

In 2000, there were 68,230 fewer CHD deaths than expected from applying mortality rates in 1981, the baseline year. The age-specific model estimates for DPPs by all interventions were compared with the observed falls in mortality in each age and sex category. The model explained 61,595 fewer deaths, representing 90% of the observed CHD mortality fall *(Chapter 9, Table 9.5).* These 61,595 fewer deaths resulted in a gain of approximately 925,415 life-years among people aged 25-84 *(minimum estimate 745,195, maximum estimate 1,138,655) (Table 10.1* and *Table 10.2).*

Life-years gained by medical and surgical treatments

Specific medical and surgical treatments for patients with CHD prevented or postponed approximately 25,745 deaths in England and Wales in year 2000[248]. They therefore gained approximately 194,145 life-years *(minimum 142,505, maximum 259,225)* in total *(Table 10.1).* The largest contributions came from secondary prevention for patients following myocardial infarction or revascularisation (32%), heart failure treatments (13%) and hypertension treatments (9%). Coronary artery bypass surgery and angioplasty proc edures together accounted for 17% of the LYGs by treatments *(Table 10.1).*

Table 0.1 Number of life-years gained by medical and surgical treatments of coronary heart disease in England and Wales in 2000.

INTERVENTION	Patients eligible	Number of DPPs*	Life-Years Gained* Best estimate (Minimum to Maximum)	%
Acute myocardial infarction	66,195	**5,750**	**38,330** (20,795 to 57,880)	**19.7%**
Secondary prevention				
Post myocardial infarction	313,380	**3,580**	**24,520** (11,900 to 37,140)	**12.6%**
Post CABG or PTCA	315,680	**3,055**	**37,660** (35,360 to 39,960)	**19.4%**
Angina				
CABG	187,415	**1,935**	**25,805** (22,550 to 31,695)	**13.3%**
PTCA	112,405	**560**	**7,905** (5,405 to 10,410)	**4.1%**
Unstable angina	72,600	**910**	**5,530** (4,700 to 9,400)	**2.8%**
Aspirin in community	2,114,665	**1,105**	**9,690 (**4,845 to 14,535)	**5.0%**
Heart failure				
Hospital treatment	41,385	**4,755**	**6,120** (4,895 to 7,340)	**3.2%**
Community treatment	242,090	**3,210**	**19,240** (7,605 to 21,140)	**9.9%**
Hypertension treatments	12,592,120	**1,890**	**17,775** (15,290 to 25,485)	**9.2%**
Statins for primary prevention	7,630,760	**145**	**1,570** (1,370 to 2,285)	**0.8%**
Total treatment effects in 2000		**25,765**	**194,145** (142,505 to 259,225)	**100%**

Life-years gained by risk factor changes in the population

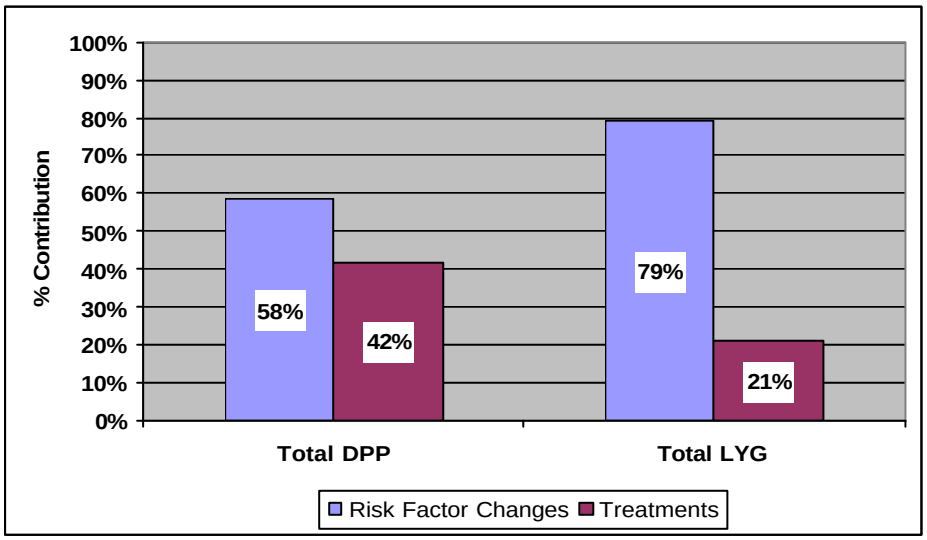
In England and Wales, approximately 35,830 deaths were prevented or postponed by risk factor changes in the population between 1981 and 2000. This accounted for some 731,270 LYGs *(minimum estimate 602,695, maximum estimate 879,430),* and represented 79% of all LYGs we estimated in 2000. The largest contribution came from reductions in smoking (54%), blood pressure (28%) and cholesterol (22%) *(Table 10.2).*

Adverse trends between 1981 and 2000 were seen for obesity, physical inactivity, and diabetes. They together caused approximately 7,650 additional CHD deaths. This resulted in a *loss* of approximately –92,640 life-years *(minimum -68,355, maximum -100,770),* effectively halving the gain from population cholesterol reductions *(Table 10.2).*

Table 0.2 Number of life-years gained by changes in population cardiovascular risk factors in England and Wales between 1981 and 2000.

POPULATION RISK FACTORS	% Change in risk factor 1981-2000	Number of DPPs*	Life-Years Gained* Best estimate (Minimum to Maximum)	%
Smoking	-34.0%	29,715	**398,080** (304,020 to 446,260)	**54.4%**
Blood pressure	-7.5%	5,870	**207,525** (197,870 to 288,445)	**28.4%**
Cholesterol	-5.6%	7,900	**164,305** (128,310 to 188,145)	**22.5%**
Deprivation	-6.6%	2,125	**53,995** (40,845 to 57,350)	**7.4%**
Obesity	+186.2%	-2,095	**-10,690** (-8,565 to -13,470)	**-1.5%**
Physical activity	- 30.6%	-2,660	**-37,055** (-27,245 to -39,450)	**-5.1%**
Diabetes	+65.6%	-2,890	**-44,895** (-32,545 to -47,850)	**-6.1%**
Total risk factor effects in 2000		**35,830**	**731,270 (602,695 to 879,430)**	**100.0%**

Figure 0.1 Comparison of deaths prevented or postponed and life-years gained from risk factor changes and treatments given to CHD patients.



Although the numbers of DPPs from risk factor changes and treatments given to CHD patients were close to each other, number of LYGs was substantially higher from risk factor changes than treatments *(Figure 10.1).*

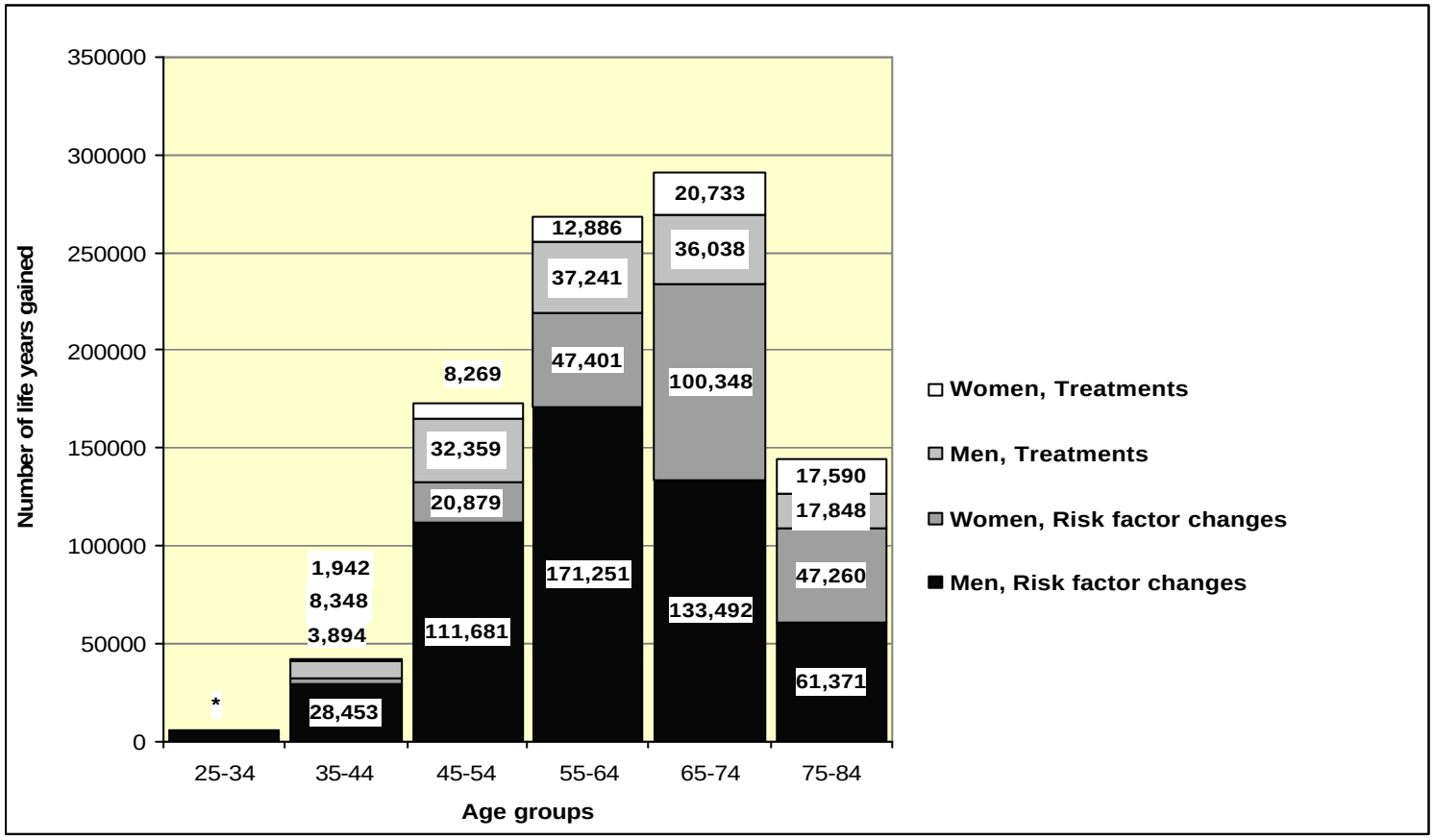
Age and sex distribution of life-years gained *(Figure 10.2)*

The majority of life-years were gained by individuals aged 55 to 74 years. More life-years were gained by men than women in all age groups; 68% (132,505 / 194,145) of the LYGs by medical and surgical treatments, and 69% (510,915 / 731,270) of the LYGs by risk factor reductions, *(Figure 10.2).*

Sensitivity analyses *(Figure 10.3)*

The relative contributions from treatments and risk factor reductions remained relatively constant, irrespective of whether best, maximum or minimum estimates were considered *(Figure 10.3).*

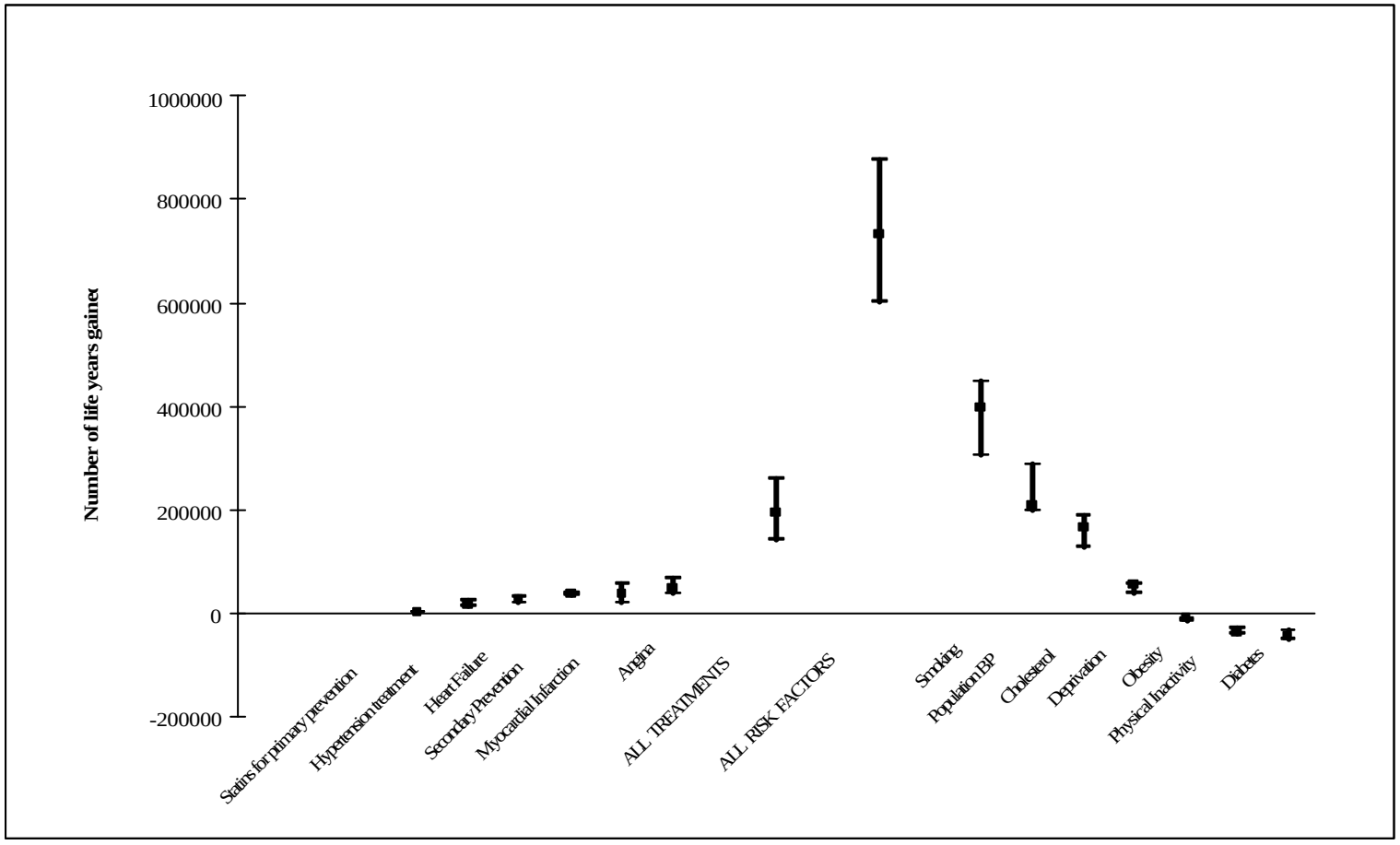
Figure 0.2 Number of life-years gained from coronary heart disease treatments and population risk factor changes, in England and Wales between 1981 and 2000 by age and sex.



Subjects aged 25-34: *Changes in **risk factors** gained 4,665 life years in men, 574 in women; **treatments** gained 672 life-years in men, 219 in women.*

Figure 0.3 Proportional contributions of specific treatments and risk factor changes to the total life-years gained from the CHD mortality decline in England and Wales, 1981-2000: Results of a sensitivity analysis.

(¦ Best estimate, - minimum and maximum estimates).



1.23 Interpretation

CHD mortality rates in England and Wales halved between 1981 and 2000. This resulted in some 70,000 fewer deaths and almost one million additional years of life. A death prevented or postponed in a patient with recognised CHD therefore gained an additional 7.5 years of life on average. Gains were greater in men, younger patients, or those surviving uncomplicated infarction, rather less in older patients or those with heart failure. In contrast, each death prevented or postponed by a risk factor reduction gained an additional 20 years of life on average, substantially more in younger individuals, rather less in older. These findings are generally consistent with previous studies[382].

Medical and surgical treatments in 2000 together gained approximately 195,000 life-years, a third from secondary prevention. Much of the remainder came from just three categories – hypertension, angina and heart failure. The LYGs from ACE inhibitors, beta-blockers and spironolactone were particularly impressive given the relatively low prescribing rates in 2000 and the high case fatality in heart failure patients[286]. This further emphasises that simple inexpensive treatments applied to all eligible patients can potentially produce huge gains[148]. Conversely, the substantial resources devoted to revascularisation in 2000 undoubtedly improved quality of life, however gains in life-years were relatively modest *(Table 10.1)*.

Risk factor reductions accounted for a 79% of total LYGs. Gains would have been even greater if there had not been adverse trends in physical activity, obesity and diabetes. These represent a major public health target for the new millennium[374]. Substantial gains came from the reduction in smoking. This highlights the rapid and substantial benefits from smoking cessation[22] and preventing people to start smoking. The UK abolition of tobacco advertising (February 2003) will be valuable383. However, additional measures will remain essential384, particularly for disadvantaged groups. Modest changes in blood pressure and cholesterol also accounted substantial LYGs. Generally risk factor changes accounted higher LYGs since these were generated in young and middle aged population.

This is the first comprehensive analysis of LYGs from risk factor reductions and cardiological treatments published for England and Wales. However, our mortality analyses are reassuringly consistent with most other studies in Europe[251], New Zealand[5] and the USA[193].

Bunker et al. examined the 7.1 years increase in life expectancy seen in the USA between 1950 and 1989[385]. Changes in coronary and cerebrovascular disease death rates accounted for 10%-20% of this increase[385]. This is consistent with our estimates for Scotland (1975-1981)[386] and for England and Wales.

Again in the USA, Tsevat et al attributed 1.0 to 1.2 years increase in population life expectancy by lowering blood pressure in men, (and 0.3 to 0.6 years in women), and 0.5 to 1.2 years by quitting smoking in 35-year old men (0.4 to 0.8 in women)[238]. Using similar assumptions, Grover et al estimated that reductions in CHD and stroke risk through blood pressure reduction would result in 0.9 to 1.2 years increase in life years in men and 0.6 to 1.3 years in women aged 40[382].

There are important implications for clinical and public health practice. In particular, the current UK government emphasis on treatments rather than risk factor reductions must be seriously questioned.

In conclusion, modern cardiological treatments in England and Wales in 2000 gained many thousands of life-years. However, four times as many life-years were generated by relatively modest reductions in major risk factors, principally smoking, cholesterol and blood pressure. Effective policies to promote healthy diets and physical activity, and reduce obesity, might therefore gain substantial numbers of additional life-years in England and Wales.

Having presented the impact of CHD treatment uptake and population risk factor changes in England and Wales, in the following two chapters, I will focus on the 'what if?' questions. What if treatments, or risk factor levels had been different?

IMPACT OF INCREASED TREATMENT UPTAKE ON CHD MORTALITY IN ENGLAND AND WALES IN 2000

In this chapter, I will explore the first "What if?" question:

'What would have been the mortality impact of increasing the uptake of cardiological treatments in England and Wales, in 2000?'

1.24 Introduction

In *Chapter 9*, I demonstrated that approximately 40% of the recent fall in CHD mortality rates can be attributed to the increasingly widespread use of effective therapies[248;373]. Furthermore, cardiology epitomises the evidence-based medicine paradigm. A wealth of evidence from randomised trials and meta-analyses underpins an expanding range of treatments including thrombolysis, aspirin, beta-blockers, statins, ACE-inhibitors, coronary bypass surgery and angioplasty[372].

However, benefit can only occur if the eligible patients actually receive the appropriate therapies[372]. Recent clinical audits and surveys suggest that treatment uptake rates remain disappointingly low for many groups of patients. For instance, following myocardial infarction, only about 25%, 44% and 56% of eligible patients receive statins, beta-blockers or aspirin respectively[269;289;349;387]. In the community, approximately 60% of angina patients are taking aspirin[289], yet barely 50% of heart failure patients receive ACE inhibitors[357]. Uptake rates are consistently worse in women, the elderly and the deprived[388].

Scope remains for substantial increases in treatment uptake; these would potentially result in large reductions in both morbidity and mortality. Recent NHS strategies including the National Service Framework for Coronary Heart Disease[148] are now beginning to address this issue. However, simultaneously tackling all these patient groups would require substantial additional resources[148;204].

I therefore examined the scale of the CHD mortality reduction potentially achievable from the increased uptake of specific medical and surgical treatments in England and Wales in 2000, in order to help identifying target groups for prioritisation.

1.25 Methods

The IMPACT mortality model was used to examine the consequences of increasing uptake of specific treatments in each category of patients. The IMPACT Model and the methods used to estimate DPPs were described in detail in *Chapter 8.*

All existing values contained within the model for the year 2000 were left unchanged (numbers of eligible patients, treatment compliance and effectiveness)[5]. The best available data on uptake of specific treatments in each category of patients, as detailed above, were used to calculate the baseline.

The potential mortality benefit if uptake was increased to reach 80% of all eligible patients, (the National Service Framework target)[148] was then calculated, assuming optimal dosing regimens. An uptake of 100% was considered unrealistic[321]. The corresponding calculation was performed for revascularisation, assuming that CABG surgery and PTCA procedures in 2000 were increased by 80%.

Sensitivity analyses

Mortality effects were analysed by age and sex. The key parameters were all subject to imprecision and uncertainty. Multi-way sensitivity analyses were therefore performed using the analysis of extremes method[341]. Minimum and maximum mortality reductions were generated using 95% confidence intervals from meta-analyses for treatment efficacy, and minimum and maximum plausible values for patient numbers, treatment uptake and adherence[341]. Information sources for number of patients, treatment uptake, treatment efficacies in IMPACT Model were presented in *Chapter 8.*

1.26 Results

In 2000, specific medical and surgical treatments in England and Wales were estimated to prevent or postpone approximately 26,000 deaths for at least one year (minimum estimate 17,110, maximum estimate 49,040) *(Table 9.1).* Some 19% of this fall was attributed to initial treatments for acute myocardial infarction, 26% for secondary prevention treatments, 31% for treatments for heart failure, and 7% for anti-hypertensive therapies *(Table 9.1).* However, uptakes were generally poor. Uptake in MI survivors averaged 56% for aspirin, 34% for beta-blockers, and 25% for statins; and for heart failure patients in the community this averaged 56% for ACE inhibitors, 17% for statins and 15% for beta-blockers *(Table 9.1).*

Mortality benefit of increasing treatment uptake to 80%

Increasing uptake to 80% of eligible patients would have prevented or postponed approximately 20,910 additional deaths at least one year (minimum estimate 11,030; maximum estimate 33,495). Of the 20,910 fewer deaths, 7,285 (35%) would have resulted from increasing heart failure treatments for community and hospital patients, and 4,680 (23%) fewer deaths from increases in secondary prevention therapies following AMI or revascularisation, *(Table 11.1).*

Extending primary prevention statin therapy to 80% of the 7.6 million healthy individuals with total cholesterol levels above 6.2 mmol/l would have prevented approximately 3,295 deaths, representing 16% of the total gain, compared with 2,370 (11%) fewer deaths from initial treatments for acute MI; 2,680 (10%) from treatments for hypertension and 1,475 (7%) from increases in aspirin and statins for patients with angina in the community.

Only 400 (2%) additional deaths would have been prevented by an 80% increase in revascularisation procedures in 2000, and just 305 (1%) fewer deaths from increases in therapies for unstable angina *(Table 11.1 and Figure 11.1).*

Table 0.1 Coronary heart disease mortality reduction in England & Wales in 2000: Effect of increasing treatment uptake to 80%

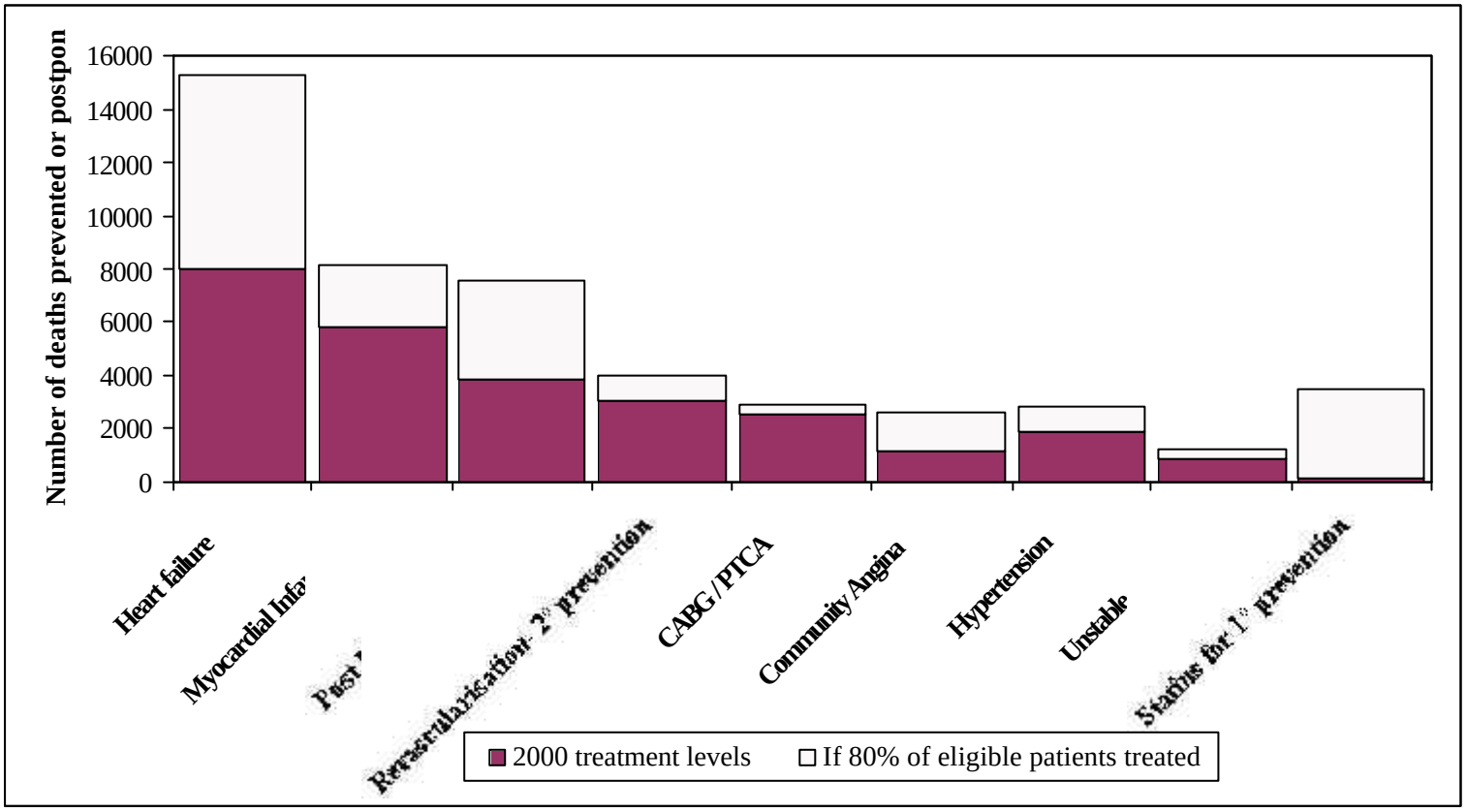
TREATMENTS	Eligible Patients	Treatment uptake in 2000	*Treatment Efficacy (RRR*)*	Deaths prevented or postponed In 2000	Gain if 80% uptake	(% total gain)	*Minimum estimate*	*Maximum estimate*
Acute Myocardial Infarction	**66,195**			**4,740**	**2,370**	(11%)	***1329***	***3414***
Community Resuscitation	3,045	0.48	0.11	800	380			
Hospital Resuscitation	7,280	0.99	0.21	1,455	-			
Thrombolysis **		0.47	0.21	1,320	50			
Aspirin		0.94	0.15	1,950	-			
Primary angioplasty***		0.01	0.28	40	1,330			
Beta-blockers		0.04	0.04	20	195			
ACE inhibitors		0.19	0.07	170	410			
2º prevention post infarction	**313,380**			**3,845**	**3,695**	(18%)	***2741***	***4865***
Aspirin		0.56	0.15	1,240	65			
Beta-blockers		0.34	0.23	970	720			
ACE inhibitors		0.19	0.23	440	915			
Statins		0.25	0.29	460	645			
Warfarin****		0.04	0.15	100	250			
Rehabilitation		0.23	0.27	675	1055			
2º prevention post revascularisation	**157,840**			**3,055**	**985**	(5%)	***561***	***1638***
Aspirin		0.56	0.15	820	100			
Beta-blockers		0.35	0.23	570	150			
ACE inhibitors		0.22	0.23	350	270			
Statins		0.34	0.29	675	205			
Warfarin****		0.04	0.15	54	115			
Rehabilitation		0.35	0.27	585	150			

*__RRR__= relative risk reduction **60% Maximum uptake assumed ***40% Maximum uptake assumed if 60% for thrombolysis
**** 20% maximum uptake assumed for warfarin if 80% on aspirin

TABLE 11.1 (continued)	Eligible Patients	Treatment uptake in 2000	*Treatment Efficacy (RRR)*	Deaths prevented or postponed In 2000	Gain if 80% uptake	(% total gain)	*Minimum estimate*	*Maximum estimate*
Angina revascularisation				**2,495**	**400**	(2%)	***270***	***560***
CABG surgery	**187,415**	1.00	0.31	1935	275		***233***	***381***
Angioplasty*	**112,405**	1.00	0.08	560	125		***36***	***181***
Unstable Angina	**67,375**			**910**	**305**	(1%)	***224***	***419***
Aspirin & Heparin		0.59	0.27	465	165			
Aspirin alone		0.30	0.15	235	0[#]			
IIB/IIIA Inhibitors & clopidogrel		0.48	0.09	210	140			
Chronic stable angina	**2,114,670**			**1,105**	**1,475**			
Aspirin		0.58	0.15	995	370	(2%)	***234***	***790***
Statins		0.07	0.29	110	1105	(5%)	***958***	***1,471***
Heart failure- in hospital	**34,690**			**4,755**	**3,350**	(16%)	***2,178***	***6,206***
ACE inhibitors		0.62	0.26	1,845	595			
Beta-blockers		0.31	0.37	1,280	1044			
Spironolactone		0.10	0.30	350	990			
Aspirin		0.50	0.15	870	119			
Statins		0.21	0.29	410	700			
Community heart failure-	**242,090**			**3,210**	**3,935**	(19%)	***1,020***	***3,048***
ACE inhibitors		0.56	0.26	1,535	34			
Beta-blockers		0.15	0.37	550	1,595			
Spironolactone		0.10	0.30	205	965			
Aspirin		0.29	0.15	585	579			
Statins		0.17	0.36	335	763			
Hypertension treatments	**13,352,870**	**0.53**	**0.11**	**1,890**	**945**	(5%)	***438***	***1586***
Statins for primary prevention	**7,630,760**	**0.03**	**0.29**	**145**	**3,295**	(16%)	***1,078***	***5,493***
TOTAL				**25,765**	**20,910**	100%	***11,030***	***33,495***

*Assuming relative risk reduction of 8%, equivalent to CABG for two vessel disease # If 80% get Heparin plus Aspirin, no option for increase in aspirin alone

Figure 0.1 Estimated CHD mortality reductions in 2000, and potential gains IF specific treatment uptakes reached 80% of eligible patients



Sensitivity analyses

The proportional contributions remained relatively consistent using an analysis of extremes approach. Irrespective of whether best, minimum or maximum values were used, the biggest potential mortality reductions came from treatments for heart failure and secondary prevention (*Figure 11.2).*

Of the total of 20,910 additional deaths potentially prevented or postponed, 12,895 (61.7 %) would have been in men and 8,015 (38.3%) in women. Two thirds of the fewer deaths would have occurred in older patients, with 7%, 15%, 22%, and 16% of the total reduction occurring in men aged 45-54, 55-64, 65-74, and 75-84 years respectively (and 2%, 6%, 14%, and 16% respectively in women, *Figure 11.3*).

Figure 0.2 Sensitivity analysis showing best estimates for mortality reductions IF specific treatment uptakes reached 80% of eligible patients.

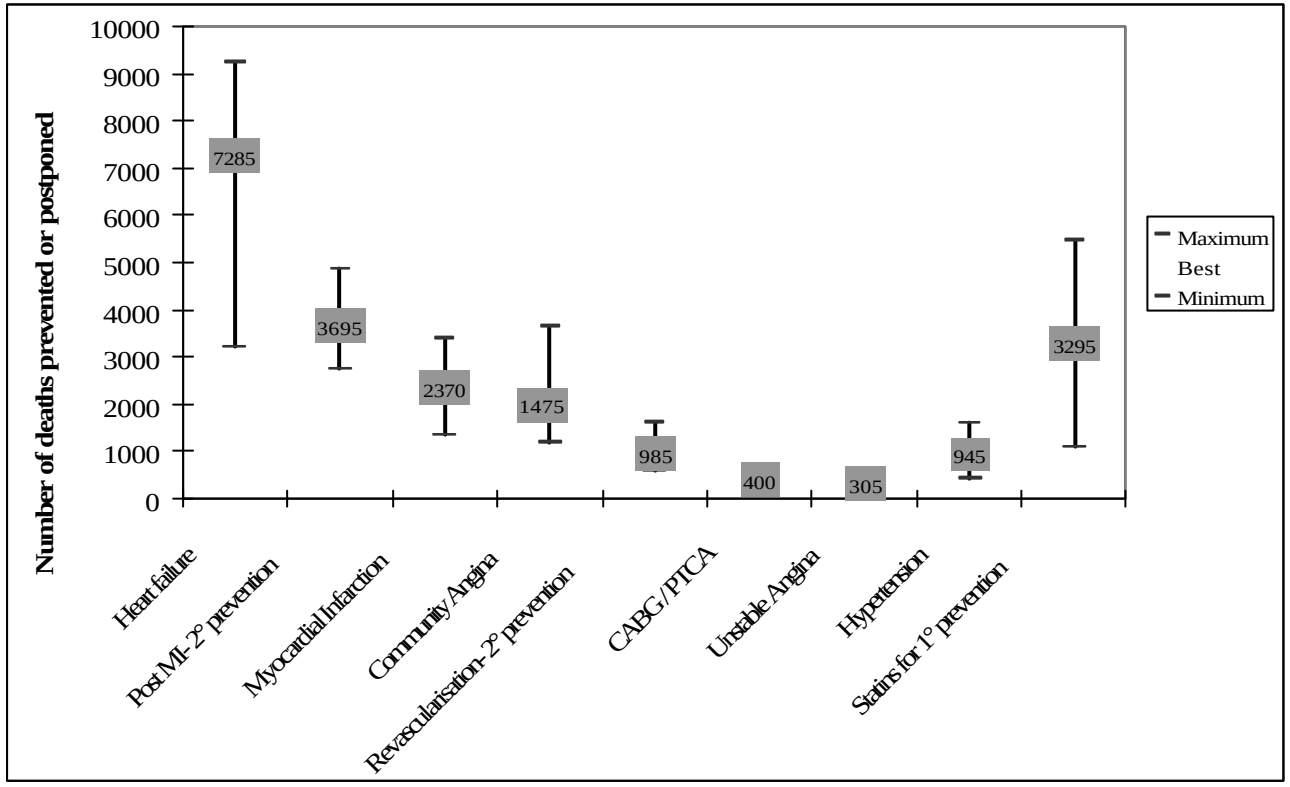
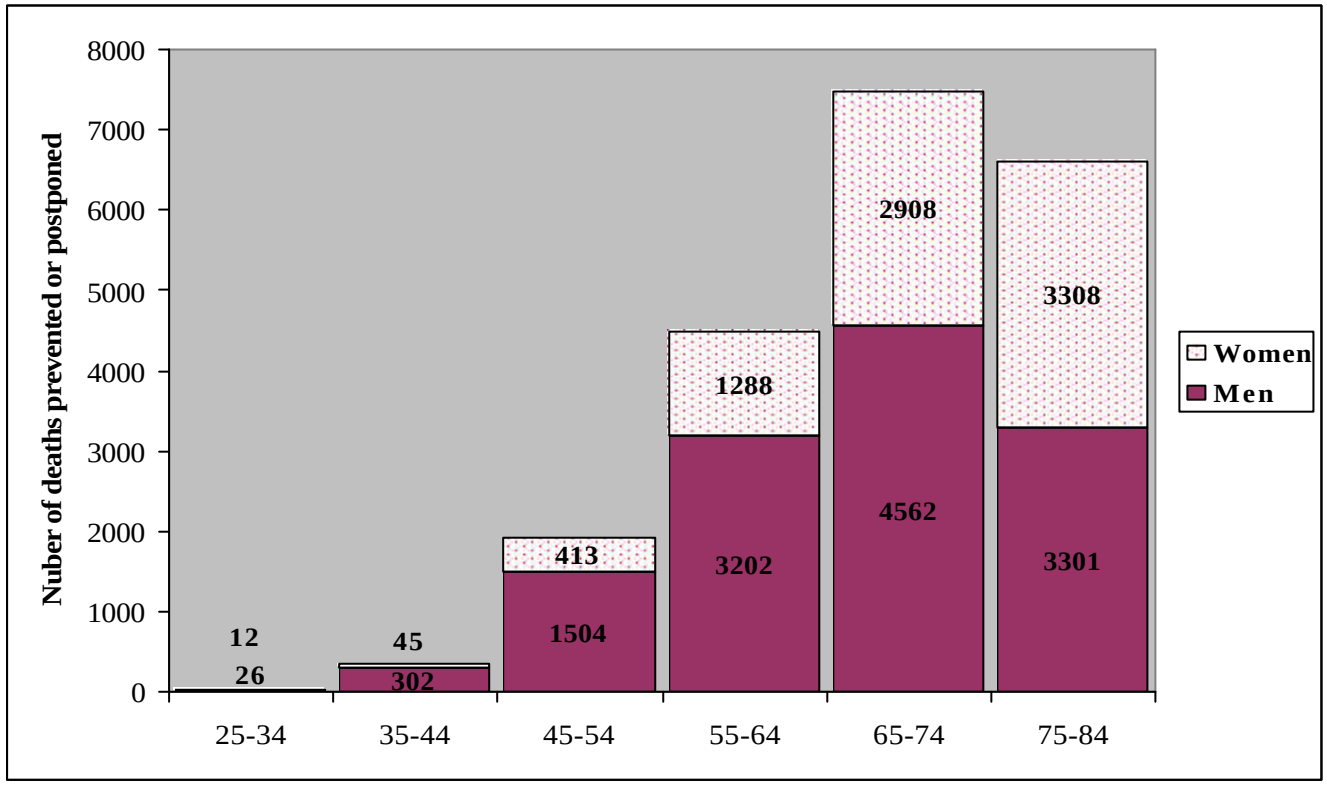


Figure 0.3 Age and sex distribution of CHD mortality reductions IF appropriate specific treatment uptakes reached 80% of eligible patients.



1.27 Interpretation

In 2000, barely half the patients with cardiac disease actually received the appropriate therapy [157;159;269;289;351;357]. If just 80% of eligible patients had received the cardiological treatment indicated, then over 20,000 extra deaths could have been prevented or postponed. This would have almost doubled the reduction in mortality achieved by treatment in England and Wales in 2000, and is consistent with other studies in Scotland and elsewhere[148;321].

But how could treatment uptakes be increased? Focused clinical audit can be effective, and has already substantially increased thrombolysis uptake rates for AMI[389], and aspirin for secondary prevention[269]. Evidence -based clinical guidelines are now widely available[390], and strategies aiming to achieve treatment uptake levels of 80% -90% have been widely disseminated[148;390].

If a strategy for increased uptake were to initially focus only on heart failure and secondary prevention, then an 80% treatment uptake would be expected to result in approximately 12,000 fewer deaths in England and Wales in 2000 (almost two thirds of the total additional benefit). However, such prioritisation would mean focusing mainly on patients in the community.

All analytical models have limitations[3;233]. The strength and limitations of the models will be discussed in detail in *Chapter 13.*

This study focused on *mortality* reduction, rather than quality of life or symptom relief. Indeed, many cardiological treatments are given principally for symptomatic improvement, such as PTCA and beta-blockers for angina, and diuretics for heart failure[148]. Furthermore, increased therapy may also reduce serious morbidity, such as myocardial infarction, stroke or heart failure often leading to repeated hospitalisation. By preventing such events, these treatments can also potentially offset their own costs [205]. At present, many patients are under-dosed, whereas maximum benefits would only come with optimal dosing [148].

In conclusion, modern cardiological treatments have already contributed substantially to the observed reductions in coronary mortality. However, a more systematic application of proven therapies to reach 80% of eligible patients would almost double the DPPs. Because resources are always limited, future strategies should prioritise the delivery of secondary prevention and heart failure therapies to all eligible patients.

SMALL CHANGES IN UK CARDIOVASCULAR RISK FACTORS LEADING TO POTENTIALLY BIG REDUCTIONS IN CHD MORTALITY?

In *Chapter 9,* I described how population risk factor changes apparently explained approximately 60% of the CHD mortality fall between 1981 and 2000. In this chapter, I will now address the very important question:

What is the potential benefit of further reductions in major risk factors?

1.28 Introduction

As I have discussed in earlier chapters, CHD mortality rates have halved in most industrialised countries since the 1980s[2]. However, mortality has declined less in the UK, and CHD remains the single largest cause of death[2]. The UK government recently endorsed CVD as a top priority[148], and in 1999, the "Saving Lives" White Paper set the target of reducing the CHD and stroke death rate in people under 75 years by at least two fifths by 2010, in other words 28,000 fewer deaths in the year 2010[374].

In this chapter I have used the England and Wales IMPACT model[248], to estimate the number of additional CHD deaths that might potentially be prevented or postponed by 2010. Initially, by simply assuming that cardiovascular risk factors continued their recent trends, and then by assuming the additional small and eminently feasible reductions already seen in many other countries.

1.29 Methods

The IMPACT model has been described in the previous *Chapters 8 and 9* in detail. Here the IMPACT model was extended from 1981 through 2000 to 2010, using population projections and mortality data for men and women aged 25-84, from the Office for National Statistics[377]. The CHD deaths expected in 2010 were calculated a) by applying the age-specific death rates in 2000 to the 2010 population, and b) by extrapolating current CHD mortality trends to the year 2010[322].

Risk factor projections

a) Assuming recent risk factor trends simply continue to 2010

Recent trends in smoking prevalence using data from the General Household Survey[200] were projected to 2010. Recent trends in total cholesterol, blood pressure, body mass index, physical activity and diabetes were obtained from the Health Survey for England, British Regional Heart Study, Glasgow-Belfast MONICA, and other UK surveys[48;125;303]. Age specific trends were extrapolated to the England and Wales population in 2010.

b) Assuming more substantial reductions in risk factors between 2000 and 2010

More substantial but feasible risk reductions were chosen, based on data from comparable populations in Europe and USA. The calculations were then repeated assuming these greater risk factor reductions.

i) ***Smoking*** The UK target to reduce smoking prevalence from the current prevalence of 26% to 24% among adults by 2010 does not appear challenging, and may be achieved simply on the basis of current trends[200;374]. An eminently feasible 2010 prevalence of 17% in all adults aged under 65, as already achieved in California in 2000[119], was therefore chosen.

ii) ***Cholesterol*** Reductions in population mean total cholesterol levels between 1981-2000 have been modest in England and Wales, less than 5% in men and women aged 45-64[125]. The annual relative falls of 1.0% in men and 1.4% in women observed in Sweden[125] were therefore applied to the British population. The projected cholesterol levels for 2010, 5.2mmol/l overall, would then simply resemble those actually achieved in the 1990s in populations such as Gothenberg (Sweden), Stanford (USA) or Perth (Australia)[125].

iii) ***Blood Pressure*** Population mean diastolic blood pressure fell on average by almost 8% between 1981 and 2000[48]. A further 4% (3.7 mmHg) decrease in diastolic blood pressure between 2000 and 2010 was examined. Such falls have already been observed in several countries including Finland (5.2 mmHg), France (6.0 mmHg) and New Zealand (4.4 mmHg)[125].

iv) ***Obesity*** *C*ommunity interventions to reduce obesity prevalence or mean BMI *in the general population* have mostly failed to achieve sustainable falls[391]. There are currently no UK obesity targets; however, a 15% reduction in obesity prevalence by 2010 was recently proposed in the USA[392]. I therefore examined the same target for England and Wales.

v) ***Physical activity*** Randomised controlled trials of rigorous, tailored interventions, generally focussed on *individual volunteers*, appear effective, with a 35% median net increase in time spent on physical activity and a net median energy expenditure increase of 64%[141]. Community interventions have generally failed to produce sustained increases in physical activity. However, a recent systematic review found that a variety of different interventions such as mass media communication and risk factor screening or counselling, increased the proportion of physically active people by 4.2%(-2.9 to 9.4) overall[141]. This may be compared with the 7%-9% increase reported in the Heart Beat Wales Programme[393]. I therefore examined the impact of a 5% potential increase in moderately active people in the England and Wales population by 2010.

vi) ***Diabetes*** Large Finnish and American studies in individuals with impaired glucose tolerance suggest that intensive individualised instructions on weight reduction, food intake and increasing physical activity can produce sustained lifestyle changes and reduce diabetes risk by 58%[394]. The main mechanisms for this risk reduction appeared to be moderate changes in body weight 3-4 kg (-5%), and moderate exercise for 150 minutes per week[394].

However these findings were from selected individuals in a high-risk group rather than the general population. In the absence of any published report of a successful reduction in diabetes prevalence in a community or population, I therefore examined the impact of 5% potential decrease in diabetes prevalence in England and Wales by 2010.

Sensitivity Analysis

Because of the uncertainties surrounding some of the estimates, a multi-way sensitivity analysis was performed using the analysis of extremes method[231]. Estimated mortality reductions were then generated using minimum and maximum plausible values for the main parameters[3-5;248].

1.30 Results

Changes in CHD mortality in England and Wales

a) Trends observed between 1981 and 2000

Overall annual declines in CHD mortality rates were 3.1% in men and 2.3% in women, ranging from 3.2% in the younger men to 1.8% in men aged 75-84 *(Table 12.1).*

b) Estimates between 2000 and 2010

Assuming that recent trends in age-specific death rates continued to 2010, approximately 86,325 deaths would be expected in 2010 (56,565 among men, 29,760 in women). This would represent an overall reduction of 23% (23% and 22% respectively in men and women) from 2000 *(Table 12.1).*

Table 0.1 Observed and projected CHD mortality rates and deaths in England and Wales, 2000-2010.

	Population (thousands)	CHD Mortality Rates/100,000		Annual Change in CHD Mortality Rates (1981-2000)	Estimated CHD deaths in 2010 with current trend	Expected CHD deaths in 2010 applying 2000 rates	Fall in CHD Deaths 2000-2010	
	a	b	c=b+(b*d*10)	d	e=a*c	f=a*b	g=e -f	g/f*100
MEN	**2010**	**2000**	**2010**	**%**	**2010**	**2010**	**number**	**%**
25-34	3,492	2.4	1.6	**-3.2**	57	84	-27	-32
34-44	4,070	18.7	12.8	**-3.2**	521	761	-241	-32
45-54	3,985	89.3	60.6	**-3.2**	2,416	3,559	-1,142	-32
55-64	3,277	282.4	199.8	**-2.9**	6,547	9,254	-2,707	-29
65-74	2,291	807.2	612.2	**-2.4**	14,025	18,493	-4,468	-24
75-84	1,287	1896.9	1563.1	**-1.8**	20,118	24,413	-4,295	-18
TOTAL	**18,402**	**213.8**	**148.0**	**-3.1**	**43,683**	**56,565**	**-12,880**	**-23**
W O M E N								
25-34	3,358	0.6	0.4	**-2.7**	15	20	-5	-27
35-44	3,855	4.5	3.4	**-2.4**	133	173	-41	-24
45-54	3,885	18.7	13	**-3.0**	506	726	-220	-30
55-64	3,342	78.4	55.3	**-2.9**	1,849	2,620	-771	-29
65-74	2,480	335.2	252.8	**-2.5**	6,270	8,313	-2,042	-25
75-84	1,700	1053.3	847.9	**-1.9**	14,415	17,906	-3,492	-19
TOTAL	**18,620**	**173.2**	**134.1**	**-2.3**	**23,188**	**29,760**	**-6,572**	**-22**
TOTAL MEN & WOMEN	**37,022**	**193.2**	**139.9**	**-2.7**	**66,830**	**86,325**	**-19,452**	**-23**

Cardiovascular risk factor changes

The risk factor levels in 2000, and the levels expected in 2010 on the basis of a) recent trends and b) more substantial reductions are detailed in *Table 12.2.*

a) Mortality reductions based on *recent trends* only *(Table 12.3)*

All three major risk factors showed declining trends between 1981 and 2000. Assuming that the same trends continued between 2000 and 2010, this would result in approximately 13,760 deaths prevented or postponed (DPPs) in 2010 (minimum estimate 9,540, maximum estimate 16,050- *Table 12.3*).

Approximately 8,880 fewer deaths would be attributable to a fall in smoking prevalence from (26% to 21%), with 2,525 attributable to a reduction in total cholesterol (from 5.8 mmol/l to 5.6 mmol/l) and 5,135 attributable to falls in population diastolic blood pressure (from 74.6 mmHg to 73.7 mmHg, *Tables 12.2 and 12.3).*

Obesity, diabetes prevalence and physical activity showed adverse trends between 1981 and 2000. Assuming the same adverse trends continued to 2010, these risk factors would cause approximately 6,980 additional CHD deaths (2,080 from obesity, 4,200 from diabetes and 705 from physical inactivity) *(Figure 12.1).*

b) *More substantial reductions* in major risk factors *(Tables12.2 and 12.3)*

A total of approximately 50,410 deaths (minimum 37,210, maximum 75,435) could be prevented or postponed by additional but feasible reductions in cardiovascular risk factors.

i) Approximately 17,060 fewer deaths assuming that the smoking prevalence fell from 26% to 17%;

ii) 24,945 fewer deaths assuming that population mean cholesterol levels declined to 5.2 mmol/l among men, and women;

iii) 6,505 fewer deaths assuming an average additional decrease in mean diastolic blood pressure of 3.7 mmHg across all age and sex groups (from 74.6 mmHg to 70.9 mmHg).

iv) 850 fewer deaths assuming a 15% decrease in obesity (a reduction from 21% to 18% in men and women by 2010).

v) 485 fewer deaths assuming a 5% decrease in diabetes prevalence (from 3.0% to 2.9% in men and from 2.1% to 2.0% in women by 2010).

vi) 1,055 fewer deaths assuming a 5% increase in the prevalence of moderately active people (from 46% to 49% in men and from 37% to 39% in women).

The number of DPPs in 2010 due to these additional risk factor changes could thus be increased more than three fold, from 13,760 to 50,410; if relatively modest improvements in adverse risk factors were achieved *(Tables 12.2 and 12.3).*

These estimates remained relatively stable when subjected to a rigorous sensitivity analysis *(Figure 12.1).*

Table 0.2 Risk factor levels in the 2000 base year and projections to 2010: a) simply continuing recent trends, b) assuming more substantial reductions achieved elsewhere *(men and women aged 25-84 years).*

Risk Factor Levels	Smoking %		Cholesterol mmol/l		Diastolic Blood Pressure mmHg		Obesity %		Diabetes %		Physically Active* %	
	Men	*Women*	*Men*	*Women*	*Men*	*Women*	*Men*	*Women*	*Men*	*Women*	*Men*	*Women*
2000	**28**	**24**	**5.8**	**5.8**	**76.9**	**72.3**	**21**	**21**	**3.0**	**2.1**	**46**	**37**
a) 2010 recent trends	**22**	**21**	**5.7**	**5.7**	**76.4**	**71.1**	**33**	**24**	**4.7**	**3.0**	**43**	**34**
b) 2010 Additional reductions	**17**	**17**	**5.2**	**5.1**	**73.2**	**68.6**	**18**	**17**	**2.9**	**2.0**	**49**	**39**

***: Moderate or strenuous activity =3 times/week for >20 minutes**

Table 0.3 The estimated reduction in CHD mortality in England and Wales between 2000 and 2010 on the basis of changes in specific risk factors: a) continuing recent trends, and b) with more substantial reductions.

RISK FACTORS	*Change in Risk Factor Between 2000 & 2010*		Deaths prevented or postponed in 2010 as a result of reductions in risk factors between 2000 and 2010 (maximum and minimum estimates)
	Men	*Women*	
Smoking			
Recent trend	*-19%*	*-16%*	8,880 (6,115 to 13,610)
More substantial reduction	***-40%***	***-36%***	**17,060** (9,810 to 30,555)
Total Cholesterol			
Recent trend	*-2%*	*-2%*	2,525 (1,530 to 4,735)
More substantial reduction	***-10%***	***-13%***	**24,945** (21,615 to 31,185)
Population blood pressure			
Recent trend	*-1%*	*-2%*	5,135 (3,850 to 6,630)
More substantial reduction	***-5%***	***-5%***	**6,505** (4,875 to 8,265)
Obesity			
Recent trend	*57%**	*6%**	-2,080* (-1,610 to -8,010)
More substantial reduction	***-15%***	***-15%***	**850** (385 to 3,425)
D*iabetes*			
Recent trend	*48%**	*30%**	-4,200* (-1,945 to -5,915)
More substantial reduction	***-5%***	***-5%***	**485** (205 to 630)
Physical activity			
Recent trend	*-2%**	*-9%**	-705* (-350 to -915)
More substantial reduction	***5%***	***5%***	**1,055** (525 to 1,370)
ALL RISK FACTORS			
Recent trend	-	-	**13,760** (9,540 to 16,050)
More substantial reduction	-	-	**50,410** (37,210 to 75,435)

**** Worsening trend producing additional CHD deaths***

Benefits stratified by age and sex, and comparison with UK targets

Overall, men would benefit more than women ('current trends' 72% of prevented deaths in men and 28% in women; 'additional reductions'60% in men and 40% in women). Approximately 24,000 fever deaths would occur in men and women aged under 75, the age group specified in the government target *(Table 12.4).*

Deaths prevented or postponed by treatments

Medical and surgical treatments in 2000 together prevented or postponed approximately 25,765 deaths[248] *(Chapter 11).* This figure might well rise to approximately 46,675 fever deaths by 2010, if the National Service Framework targets are achieved, with at least 80% of eligible patients receiving appropriate therapy[395]. This would therefore represent approximately 20,000 fewer deaths than in 2000.

SENSITIVITY ANALYSES

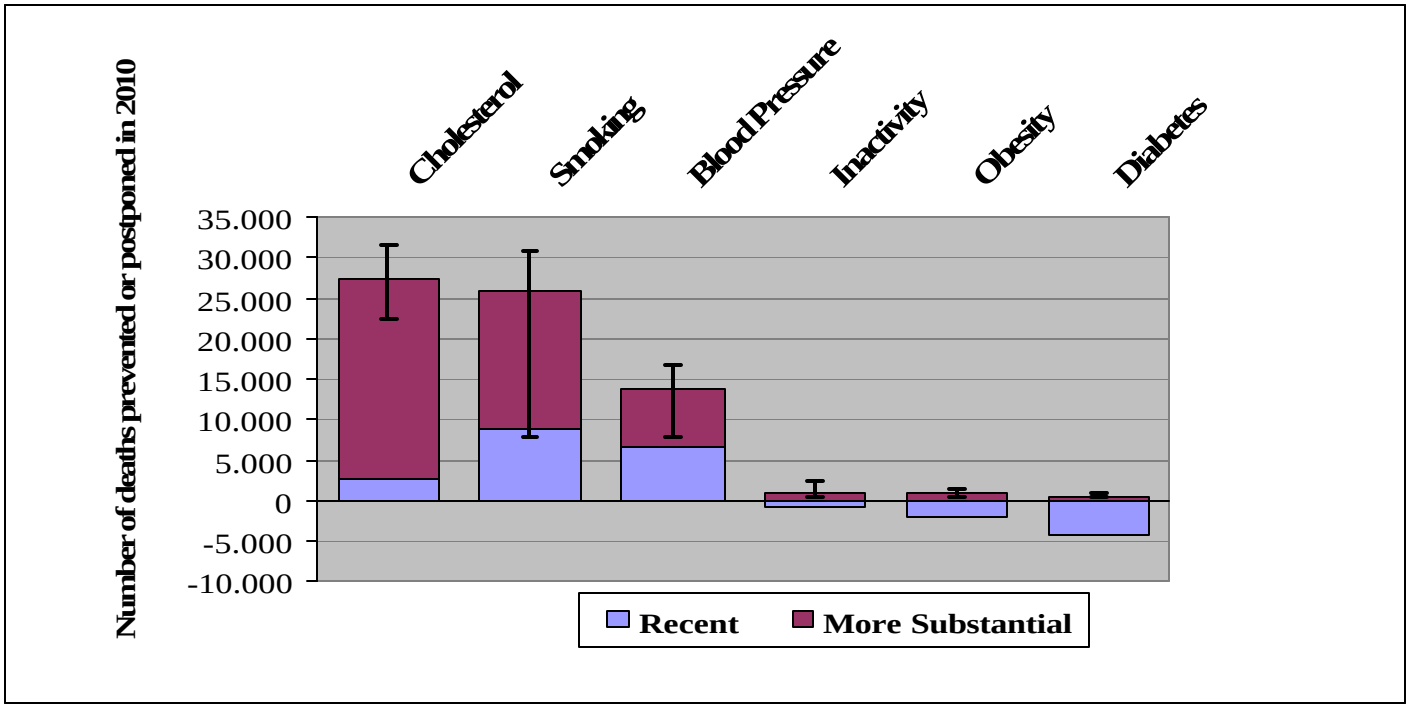
There is a consistently huge potential gain from cholesterol reductions in the population. Large DPPs can be achieved also from smoking reduction in the population. Furthermore, DPP gains from smoking can range from as little as 9,810 to very substantial higher values (30,555) (Figure 12.1).

Table 0.4 Reductions in CHD mortality achievable in 2010, stratified by age and sex a) continuing recent risk factor trends and b) with more substantial risk factor reductions.

	Deaths prevented or postponed			
	Men		Women	
	Number	%*	Number	%*
25-34 years				
Recent trends	3	*0%*	2	*0%*
More substantial reduction	60	*0%*	10	*0%*
35-44 years				
Recent trends	180	*1%*	30	*0%*
More substantial reduction	725	*1%*	140	*0%*
45-54 years				
Recent trends	855	*6%*	125	*1%*
More substantial reduction	3,145	*6%*	720	*1%*
55-64 years				
Recent trends	1,345	*10%*	475	*3%*
More substantial reduction	4,115	*8%*	1,420	*3%*
65-74 years				
Recent trends	2,490	*18%*	1,505	*11%*
More substantial reduction	8,560	*17%*	4,995	*10%*
75-84 years				
Recent trends	5,070	*37%*	1,685	*12%*
More substantial reduction	14,035	*28%*	12,485	*25%*
Total				
Recent trends	**9,935**	***72%***	**3,820**	***28%***
More substantial reduction	**30,635**	***60%***	**19,775**	***40%***

* Over total DPPs gain from recent trends (13,760) and more substantial reductions (50,410).

Figure 0.1 Potential change in CHD mortality in England and Wales between 2000 and 2010 if risk factors a) continue recent trends b) undergo more substantial reductions.



(Bars indicate maximum and minimum estimates from the sensitivity analysis).

1.31 Interpretation

Surprisingly modest risk factor reductions could prevent or postpone over 50,000 CHD deaths in 2010 in the UK. This would represent half the 100,000 current annual coronary deaths[2], and would include some 24,000 fewer premature deaths (aged under 75), as specified in recent government targets.

The biggest potential CHD mortality reductions in the UK would come from decreases in blood total cholesterol: with a 2% - 4% mortality reduction for every 1% decrease in cholesterol[32]. Yet actual falls in UK total cholesterol have been modest, and current levels remain higher than most of the other Western countries[2]. This is not surprising given the lack of coherent dietary policies in the UK. As I have previously emphasised in *Chapter 3*, elsewhere, complementary national and local programmes have achieved substantial dietary changes[123;124].

I found that each percent reduction in UK smoking prevalence would result in some 2000 fewer CHD deaths each year. The recently approved WHO Framework Convention for Tobacco Control has again emphasised the two essential comprehensive strategies: preventing young people from commencing to smoke, and promoting cessation in smokers[396]. In most of the Scandinavian countries, advertising bans were found to be effective in lowering tobacco consumption[117]. In the USA intensive health promotion and taxing programmes resulted in more impressive declines, which slowed visibly when these programmes were suspended[119].

A 1% reduction in UK population diastolic blood pressure, continuing recent trends, would prevent over 5,000 CHD deaths in 2010. This is because recent relative changes in mean diastolic blood pressure in older age groups were substantial, up to 8%. Thus, assuming a reduction of 5% in all age-sex groups, as seen in Scandinavia, would have surprisingly little additional impact, (approximately 6,505 DPPs overall). Population blood pressure has been decreasing in many Western countries in recent decades[125]. Much of this has been attributed to the reduced intake of preserved foods. Dietary salt restriction clearly achieves a small blood pressure reduction in normotensive subjects, and even more in hypertensives, about 4 mmHg systolic / 2 mmHg diastolic[126] *(Chapter 3).*

The recent UK increases in inactivity, obesity and diabetes are responsible for over 7,000 CHD deaths each year. Effective interventions to change these risk factors in the population

are discussed in *Chapter 3*. Systematic reviews of mostly US studies suggest that *in individuals*, exercise interventions promoting walking are more successful than those requiring attendance at a facility[142]. The most effective intervention for *obese individuals* is apparently a combination of advice on diet and exercise, supported by behavioural therapy[138]. In the *population*, obesity reduction appears challenging whereas several interventions clearly increase physical activity. These include community wide campaigns, school based interventions and individually adapted health behaviour change programmes[141]. Furthermore, transport policies that promote walking and cycling may play a major role. No government obesity targets have yet been set. The recommendations by the ongoing Health Select Committee enquiry are eagerly awaited.

The strengths and limitations of the model are discussed in detail in *Chapter 13*. In addition a number of further assumptions were made to estimate the number of deaths that could be prevented with additional risk factor reductions. For example, I assumed that major risk factors might continue to change at similar annual rates until 2010, and that coronary mortality would continue to decline at current rates. Extensive sensitivity analyses were therefore required to consider higher and lower values for each estimate[231]. These modestly influenced the number of DPPs, but did not alter the relative contribution of each risk factor *(Figure 12.1)*.

Furthermore, our findings are generally consistent with a recent report on monitoring the 2010 CHD target[336]. This report suggested that reducing mean population cholesterol level to 5 mmol/l or less would prevent approximately 50% of CHD deaths. An (optimistic) 25% reduction in the prevalence of obesity or inactivity might prevent 2% and 1% of CHD deaths respectively[336].

In conclusion, the government's "Saving Lives" target therefore appears eminently achievable and distinctly unchallenging. However, Britain lags behind many other counties and CHD will remain the biggest cause of death for the foreseeable future. Furthermore, continuation of current trends cannot be assumed, particularly given the 'levelling off' in CHD mortality recently seen in the USA[397].

The policy implications of these findings will be discussed in the next chapter.

DISCUSSION

1.32 Main findings

In my thesis, I first evaluated the data sources available for CHD in the UK. Data were varied in quality. Population and patient data were usually available and accessible from official statistics. Risk factor data were limited for the early 1980s but more extensive by 2000. Data on hospital interventions were not routinely available, but limited prescribing and uptake data for primary and secondary care were available. In general, data for women and the elderly (over 65) were particularly scarce and variable in quality.

Using these available data, I then explored the CHD burden in England and Wales. In 2000, an iceberg of disease was apparent in the England and Wales population of 51 million, with approximately 60,000 patients undergoing revascularisation, over 2.5 million patients living with CHD and over 32 million possessing one or more elevated risk factors *(Chapter 4).*

CHD mortality fell by more than half between 1981 and 2000 in England and Wales. In my thesis, I therefore transformed and developed the IMPACT model to explore this decline. Approximately 40% of the fall was attributable to the combined effects of modern cardiological treatments, whereas almost 60% was attributable to reductions in major risk factors *(Chapter 9).* These findings were consistent with the majority of other studies that used diverse methodologies in the USA[193], Europe[251], Scotland[4], and New Zealand[5]. Thus in the US population, for instance, 50% of the recent CHD mortality decline was actually explained by risk factor reductions[233].

Modern cardiological treatments prevented or postponed approximately 26,000 deaths in 2000 in England and Wales. The most substantial contributions came from secondary prevention therapies and heart failure treatments. This is not surprising, because improvements in survival after acute coronary events in the last decade have been documented in many countries, including England and Wales[249] , thus potentially increasing the number of patients eligible for secondary prevention.

Reductions in the major risk factors between 1981 and 2000 accounted for approximately 36,000 fewer deaths in England and Wales in 2000. The biggest single contribution reflected a large fall in smoking prevalence, from 39% to 28% overall. Almost 10% of the mortality fall came from a relatively small reduction (4.2%) in population total cholesterol level. This

emphasises the potential gains from bigger reductions in population cholesterol, with a 2% - 4% mortality reduction for every 1% decrease in cholesterol[32].

In my thesis, I then estimated life-years gained (LYGs) from cardiovascular risk factor reductions and cardiologic al treatments. This is the first comprehensive analysis of life years gained from risk factor reductions and cardiological treatments published for England and Wales. The fall of 69,000 DPPs corresponded to almost one million additional LYGs in the same period. Surprisingly, cardiological treatments explained only 21% of this gain, mostly from secondary prevention and angina treatments. Although heart failure treatments resulted in over 7,700 DPPs, because of the short life expectancy in these patients, only 25,360 LYGs (or 2% of overall LYGs gained by cardiological treatments and population risk factor changes in England and Wales, in 2000) might actually be gained[248;264]. Almost 80% of the LYGs came from changes in population risk factors, principally smoking, but also cholesterol and blood pressure *(Chapter 10).*

A death prevented or postponed in a patient with recognised CHD gained an additional 7.5 years of life on average. Gains were greater in men, younger patients, or those surviving uncomplicated infarction, rather less in older patients or those with heart failure. In contrast, each death prevented or postponed by a risk factor reduction gained an additional 20 years of life on average, substantially more in younger individuals, rather less in older people. These findings are generally consistent with previous studies[382]. However these LYGs occurred in people whose deaths due to CHD was prevented or postponed, rather than in the whole population. However, population life expectancy might also be increased. Bunker et al. examined the 7.1 years increase in life expectancy observed in the USA between 1950 and 1989. Changes in coronary and cerebrovascular disease death rates accounted for 10%-20% of this increase[385]. This is consistent with estimates for Scotland (1975-1981)[386]. Again in the USA, Tsevat et al attributed 1.0 to 1.2 years increase in population life expectancy by lowering blood pressure in men, (and 0.3 to 0.6 years in women), and 0.5 to 1.2 years by quitting smoking in 35-year old men (0.4 to 0.8 in women)[238]. Using similar assumptions, Grover et al estimated that reductions in CHD and stroke risk through blood pressure reduction would result in 0.9 to 1.2 years increase in life years in men aged 40, and 0.6 to 1.3 years in women[382].

In 2000, barely half the patients with CHD actually received the appropriate therapy in England and Wales. I therefore further explored potential benefits from increasing treatment

uptake levels. If just 80% of eligible CHD patients had received the cardiological treatment indicated for them in evidence-based guidelines, then a further 20,500 deaths could have been prevented or postponed. This would have almost doubled the reduction in mortality actually achieved by treatments in England and Wales in 2000 *(Chapter 11)*. The largest contributions would come from increasing heart failure and secondary prevention treatments to 80%. Furthermore, such prioritisation would mean focusing principally on patients in the community. These findings were consistent with previous studies[321]. Furthermore, as discussed in *Chapter 11*, they highlighted the need to identify effective strategies for increasing treatment uptake.

In *Chapter 12*, I considered the number of additional CHD deaths that might potentially be prevented or postponed by further reductions in major cardiovascular risk factors. Firstly assuming that cardiovascular risk factors simply continued their recent trends to 2010, and then by assuming the additional small and feasible reductions already seen in several other countries. The modest additional risk factor reductions already achieved in Scandinavia and the USA could potentially prevent or postpone over 50,000 CHD deaths in 2010 in the UK. This would halve the 100,000 current annual coronary deaths. However, I only estimated the impact of population risk factor change without considering in detail how these levels could be achieved. There is ongoing debate about whether to target high-risk people or the whole population for risk factor interventions. Kottke et al modelled these two interventions to compare the expected benefits from high-risk and population strategies, using Monte Carlo simulation[398]. They used actually achieved cholesterol and blood pressure changes without drug treatment in North Karelia between 1972 and 1977[399]. They found that a 4% reduction in cholesterol, 3% reduction in DBP and 15% reduction in smoking prevalence in the whole population would lead to 12% decrease in nonfatal MI, and 18% decrease in CHD deaths in the US[398]. However, just targeting people who have 3 risk factors with high levels and reducing their cholesterol to 180 mg/dl (or 4.7 mmol/l), diastolic blood pressure to 80 mmHg and eliminating smoking would reduce nonfatal MI by 2% and CHD death by only 5% in the US[398]. Their findings were similar for Finnish North Karelia cohorts[398]. It has been consistently suggested by Rose and others that in populations with a relatively high incidence of CHD, such as England and Wales, targeting entire population would produce larger effects than focusing on high-risk populations[188;398].

1.33 Strengths of the IMPACT Model

This study used a cell-based mortality model, which has been tested and refined over a number of years in several different populations[4;5;321;322;386]. It was extensively developed over the three years of my PhD studentship. The IMPACT Model can now generate estimates for DPPs and life years gained for England and Wales population. Furthermore it can estimate potential gains from further treatment increases[320] or risk factor reductions[322].

In this thesis, I have described the further development of the original IMPACT Model to include new treatment options and risk factors. This has made the IMPACT Model quite comprehensive. Despite its size, the IMPACT Model is user friendly, as it is based in a common spreadsheet package, Excel, and therefore easy to update with new data or to add new treatment options or risk factors.

The IMPACT Model is the first comprehensive CHD mortality model for whole population of England and Wales. In this thesis, I used the model to consider questions relevant to public health policy and CHD NSF[148].

The model incorporated large amounts of data from various selected best available sources. Data quality was assessed first, and missing or incomplete data were dealt with by extrapolation or explicit assumptions. The assumptions used in IMPACT Model were documented and tested. Comprehensive sensitivity analyses were then carried out to explore these limitations.

Comparing with other major models in Table6.2, the IMPACT model satisfies most of the quality criteria recommended in the ISPOR Guideline216. The IMPACT model considers risk factors and categories of CHD and treatment options in a coherent model. Few of the models reviewed in Chapter 6 considered risk factors and treatments together. Furthermore, IMPACT's internal validity was extensively checked by two other researchers (SC, JC).

The IMPACT Model estimates were then validated by comparison with the observed reductions in CHD deaths in England and Wales, stratified by age and sex. This method appears acceptable since IMPACT is a descriptive model. External validity or predictive validity may be considered desirable but not be essential for this kind of model 215;216.

The validity of this model could be further evaluated using different models for the same question[215], such as PREVENT or CHD Policy Model (corroboration). However this might well require considerable time and effort.

All modelling studies include a number of assumptions, which need to be clear and well documented for the users. The assumptions used in IMPACT Model were tested and documented.

1.34 Limitations of the IMPACT Model

CHD Data input

All modelling studies have limitations. Models are based on large amounts of data from many sources. However available data may be mixed in quality and lacking in quantity. In case of the IMPACT model, UK CHD data sources lacked precise data for some of the risk factor changes and patient numbers. However, to a certain extent it was possible to extrapolate some of the missing data. This was the case for diabetes and cholesterol trends since data were not available for the beginning of 1980s.

I also needed to make a number of explicit assumptions to cover deficiencies in the UK data on CHD[206]. This was essential for age specific treatment uptake levels for hospital CHD care, and some of the risk factors in the early 1980s such as blood pressure and cholesterol. Furthermore, different sources reported slightly different uptake levels or risk factor levels. In such cases, I choose the most "reasonable" source after critical consideration of all alternative sources. In modelling studies uncertainties in some data are unavoidable. However, sensitivity analyses are extremely useful to quantify the degree of uncertainty and hence the potential bias. I therefore used rigorous 'analysis of extremes' sensitivity analysis methodology to examine these uncertainties in data[231]. Reassuringly, the relative contribution of each risk factor and treatment to the overall CHD mortality decline was little changed whether considering best, minimum or maximum estimates *(Figure 9.2).*

When I started to build the IMPACT Model for England and Wales, I aimed to include all age groups over 25. However, risk factor and treatment data for people over 85 years were very limited. Therefore, my final model only included the age groups 25-84. The model fit was also not so good in older women, aged 75-84 years. This probably reflects less satisfactory data quality, particularly less accurate coding for cause of death (Table 9.5)*[157;183]*. The elderly

population is increasing, and as they will have higher health care needs, it is very important that modelling studies in the future should explicitly include these groups. Fortunately, in the UK and other comparable countries more data have become available for elderly people in 1990s[400].

Model Outcomes

At the moment, the IMPACT Model focuses only on mortality and LYGs. A recent attempt was made to include cost and cost-effectiveness of the treatments for CHD in England and Wales in 2000[401]. Future work should also focus on converting LYGs in to quality adjusted life years (QALYs), and estimating the cost-effectiveness of interventions for primary and secondary prevention strategies. It would also be desirable to include outcomes such as the incidence of CHD or symptomatic relief. Some CHD policy models have included a wider range of outcomes. For instance, the CHD Policy Model can generate estimates for many outcomes such as incidence of CHD events, CHD prevalence, CHD mortality, life years gained, cost per life year and all cause mortality[222]. However that model does not include all individual CHD treatment effects.

The IMPACT model was confined to CHD, and did not explicitly consider patients with other CVD such as stroke or peripheral arterial disease. Neither does IMPACT consider the development of other diseases or "competing causes" such as cancer[373]. However, since many cancers share some CHD risk factors such as smoking, interventions for reducing smoking would actually decrease deaths from lung cancer and other cancers[2;119;156].

The original Scottish IMPACT Model only included three major risk factors - smoking, cholesterol and blood pressure. I therefore introduced new risk factors including diabetes, obesity, physical inactivity and deprivation to the IMPACT Model for England and Wales. This improved the model fit substantially and now IMPACT Model explains 89% of the mortality fall. Furthermore, it has been estimated that these major risk factors explain approximately 85% of the UK variation in CHD risk [333]. However, other independent risk factors, such as dietary antioxidants, homocysteine and the birth weight, could be included to increase comprehensiveness.

Methodology

Certain methodological issues merit further attention in the IMPACT Model. Risk factor lag times were not explicitly considered. For many carcinogens, the delay between exposure to a carcinogen and overt disease may be decades, however, lag times for CVD are much shorter[366]. Lag times may therefore be relatively unimportant over a 20-year analysis of CHD, because mortality reduction occurs relatively quickly, within 1-5 years of quitting smoking or reducing cholesterol[22;32].

Assumptions

The IMPACT Model used β coefficients to estimate impact of risk factor changes on CHD mortality. Assumptions were made that benefits from concomitant risk factor reductions are "independent" therefore DPPs from each risk factor could be summed. All the beta coefficients and relative risk values were obtained from multivariate logistic regression analyses and therefore adjusted for potential confounding from the major risk factors. However 'residual confounding' from other potentially important risk factors for CHD, including diet (such as consumption of fish oils anti-oxidants and alcohol), and life-course factors and some novel risk factors may remain. These estimates may therefore still overestimate, because most multivariate regression models, of necessity, included data on only a limited range of risk factors. For the MONICA study, for instance, these were smoking (yes or no), systolic blood pressure, total cholesterol, and body mass index[125]. Further development work is clearly needed[3].

The IMPACT model also assumes that efficacy, the mortality benefits reported in randomised controlled trial patients can be generalised to effectiveness in unselected patients in clinical practice. Though not ideal, this appears acceptable[402]. A consistent treatment effect independent of the level of risk is also assumed, again, perhaps not unreasonably[402].

Sensitivity analyses were essential to examine the effect of varying these underlying assumptions, and hence test the robustness of the model[231]. Maximum and minimum estimates were sometimes wide. However, the relative contribution of each individual intervention remained remarkably consistent. Thus the major potential gains from *treatments* generally came from heart failure and secondary prevention, followed by initial treatments for myocardial infarction and statins. Correspondingly, the largest risk factor impacts always came from smoking and cholesterol, *(Figure 9.2, Figure 10.3, Figure 12.1).*

1.35 How can CHD modelling be improved?

Modelling is potentially very useful for health policy decision-making. However not all the models are equally suitable for this purpose. Modelling in health is a relatively new scientific field. As model users and developers increase and become more experienced, so modelling standards should also improve as validation becomes routine.

First comes internal validity. The technical accuracy of models must be verified to ensure that the model performs all the calculations correctly. Data entry errors and logical inconsistencies can all be detected during verification[218].

External validation is also becoming more straightforward. Recently published guidelines now provide basic principles for modelling[216;220;226]. Furthermore, such guidelines are not prescriptive; they simply attempt to systematize the components of the model and the information needed for model development. Clearly, different circumstances may lead to deviations from these guidelines, depending on the purpose of the model and on resources available (time, data, money). However, promoting and publicising 'best practice principles for managing models, (whether based on spread sheets or on other methodologies) is likely to increase their user friendliness, acceptability and credibility [226].

How can we improve the IMPACT model?

A number of improvements should be considered:

- Including different outcomes, such as the QALY. This could be achieved by applying published QALY weights to specific patient groups.
- Including CHD events (incidence) or 'number of surgical interventions such as CABG and PTCA avoided' as an outcome. This could be done with more reliable data on these outcomes as they become available
- Including new treatments and risk factors. The model can then be updated as new effective treatments become available. It could also be updated with trend data on new risk factors as these become available, for instance low birth weight, or specific dietary factors.
- Consultations between the developers, the potential users of the IMPACT Model and one or more IT specialists could improve the user friendliness of the model. For instance, a more user-friendly "front end". The IMPACT Model could start with a brief introduction, portfolio of exercises, and options to test and compare different policy options. This could

perhaps be achieved by incorporating macros, which could save some columns in the currently large model spreadsheet.

- The original Operational Manual for the IMPACT Model was created by our team (SC, JC, BU) and used by collaborating researchers. A revised and updated manual would potentially be very useful to introduce new users to the basic methodology of the model.

1.36 Implications for public health practice

The National Service Framework for Coronary Heart Disease now requires primary care disease registers in every practice. Such registers will certainly help to identify eligible patients, but will require substantial resources[148]. Furthermore, it is unclear whether registers alone will substantially increase treatment uptakes [403]. The National Service Framework for Coronary Heart Disease also requires practices to establish 'cardiac prevention clinics' run by trained nurses and supported by a doctor. Structured care should be provided in these clinics for the patients with CHD. It is recommended that by April 2002, the use of effective medicines after heart attack (especially use of aspirin, beta-blockers and statins) should be improved so that 80-90% of people discharged from hospital following a heart attack will be prescribed these drugs. However, no clear milestones were set for patient care in the population [148]. These recent government targets, combined with financial incentives in the new GP contract, may also have positive effects[404]. Greater patient empowerment may also be required[148].

1.37 Policy implications for decision makers

This modelling work provided potentially very useful information for health policy makers. It demonstrates that risk factor changes consistently prevented more deaths and saved more life-years in the general population than treatments. This is mainly because the number of individuals eligible for each treatment was much smaller compared than the number of subjects potentially eligible for risk factor changes using the 'population approach'. Some interventions offer only small benefits to individual subjects; however, when applied to large numbers of people they produce significant health gains for the population and this is known as *prevention paradox*[188]. This emphasises the importance and potential of primary prevention strategies. Interventions should therefore target the whole population, and should be comprehensive. Tobacco taxation plus legislation on smoking restrictions in public places, green transport policies and diet interventions can all be particularly valuable. Such policies

could produce further substantial reductions in coronary mortality, as already achieved elsewhere[119;125;192]. However in the CHD NSF this population approach was rather overshadowed by the individual patient care perspective. Periodic risk factor evaluation for the individuals was recommended with interventions directed to high-risk people rather than the whole population[148].

1.38 Clinical implications

This thesis also produced potential useful findings for the clinical management of CHD. Treatments for the secondary prevention of CHD prevented or postponed more deaths than any other intervention in CHD patients. Heart failure therapies also had a major effect, particularly surprising given the often poor prognosis of heart failure in many patients.

Revascularisation from CABG surgery and angioplasty surprisingly accounted for only a very small part of the mortality fall and gains in life-years. Similar findings have been reported from other countries such as the USA[375]. This is a disappointingly small contribution, considering the large financial and political resources being consumed to promote revascularisation[148;205]. However, it is important to remember that this thesis has considered only mortality and life years gained as outcomes. Revascularisation might be more effective at relieving anginal symptoms than medical treatments such as beta-blockers, nitrates and calcium channel antagonists[151].

The LYGs from ACE inhibitors, beta-blockers and spironolactone were relatively large, given the relatively low prescribing rates in 2000 and the high case-fatality in heart failure patients[286]. This further emphasises that simple inexpensive treatments applied to all eligible patients can potentially produce huge gains[148].

1.39 Research implications and future research questions

1) One of the future research questions is related to the modelling methodology. At present I assume that risk factor reductions are independent, as discussed above. It would be worthwhile to explore how much difference does **clustering of risk factors** make and whether the reductions principally occur in subjects with many or only one risk factor.

2) CHD mortality did not fall equally in all social classes. It would therefore be desirable to evaluate the risk factor trends in these groups and explore their impact on mortality change.

3) More effective methods are needed for changing risk factor distributions in the whole population. There is currently a lack of evidence for some factors, including physical activity, diabetes, and obesity.

4) This thesis emphasised effective strategies to reduce CHD mortality in England and Wales. Liaison with local and national policy makers to increase the utility of the model is therefore very important. Several people and groups who worked in various levels of NHS have consulted us to use the model to answer different questions in their practice. We offered training and collaboration, because the model was not sufficiently user friendly to let them use it unaided. Future work should therefore involve efforts to increase the user friendliness of the IMPACT Model, as described above.

1.40 Lessons I have learned

- While building a model, it is very useful to keep a diary, because modelling is an iterative process.
- A list of data and the sources used in the model should be prepared and updated frequently with evaluation, strengths and weaknesses of the sources.
- Building the model involves a lot of teamwork. Good cooperation and communication between the team members is crucial. Regular meetings and supervision can be very helpful.
- There should be also some agreement between the team members on the ways of working on the model. These may involve more practical actions for example writing the formulas in a certain way, not putting the same data source in the spreadsheet more than once but linking it if it is necessary or using the same colour code for some estimates. A 'best practice points' list was suggested by Edwards et al[226] *(Appendix 12).*
- Teamwork is also important for model verification to check the model for erroneous data entries and formulas.

- While building a model, it is important always to keep electronic back-ups on different computers, since a virus attack or a technical problem can destroy the product of long and painstaking work.

1.41 Conclusions

CHD represents a massive burden of disease in England and Wales. Yet information on CHD is quite patchy and poor. Future CHD disease monitoring and evaluation therefore will require more comprehensive and accurate population-based information on trends in patient numbers, treatment uptake and risk factors. This will require adequate resources to improve existing information systems. Regular and comprehensive surveys (including women and elderly people), using standardised methodology will also be essential.

CHD mortality in England and Wales fell by more than half between 1981 and 2000. Over half this fall was attributed to reductions in major risk factors, and some forty percent to medical therapies. This fall in CHD mortality resulted in almost one million additional years of life. Modern cardiological treatments in England and Wales in 2000 gained many thousands of life-years. However, three times as many life-years were generated by relatively modest reductions in major risk factors, mainly smoking, cholesterol and blood pressure.

In the year 2000, treatment uptake levels were generally poor. Increasing uptake levels to reach 80% of all eligible patients would have almost doubled the deaths actually prevented or postponed. The largest benefits would have come from heart failure and secondary prevention treatments. Furthermore, if the UK managed the modest additional risk factor reductions already achieved in the USA and Scandinavia, this could prevent or postpone substantial numbers of deaths, potentially halving the current coronary mortality by 2010. Cholesterol and smoking reductions would provide the largest gains.

These findings therefore emphasise the importance of a comprehensive strategy which actively promotes primary prevention, particularly for tobacco and diet, and which maximises population coverage of effective treatments, especially for secondary prevention and heart failure.

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APPENDICES